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CEREBRAL HEMISPHERES OF THE AMERICAN BLACK BEAR (URSUS AMERICANUS)

MORPHOLOGIC AND PHYLOGENETIC CHARACTERISTICS

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Much search through the literature has failed to bring to light any adequate description of the brain of the Ursidae, or bear family. Especially meager are the figures and descriptions of the central nervous system of the American black bear (Ursus americanus). The morphologic and phylogenetic aspect of the cerebral hemispheres has been almost completely neglected. Up to this time the brain of Ursus americanus has been only briefly described or illustrated by Wilder,[1] Krueg,[2] Elliot Smith[3] and Papez.[4] In a similar manner these and other investigators, namely, Leuret,[5] Gratiolet,[6] Gervais,[7] Meynert,[8] Mivart,[9]

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1. Wilder, B. G.: The Outer Cerebral Fissures of Mammalia (Especially Carnivora) and the Limits of Their Homology, Proc. Am. A. Adv. Sc. 1873, p. 214.

2. Krueg, Julius: Ueber die Furchen auf der Grosshirnrinde der zonoplacentalen Säugethiere, Ztschr. f. wissensch. Zool. **33**:595, 1880.

3. Smith, G. E.: Catalog of the Royal College of Surgeons, Physiol. Ser., ed. 2, 1902, vol. 2.

4. Papez, J. W.: Comparative Neurology, New York, Thomas Y. Crowell Company, 1929.

5. Leuret, F. and Gratiolet, L. P.: Anatomie comparée du système nerveux, considérée dans ses rapports avec l'intelligence, Paris, J. B. Baillière & fils, 1839-1857.

6. Gratiolet, Pierre: Observations sur les propositions que M. Dareste a soumises à l'Academie des Sciences, touchant les circonvolutions du cerveau, Rev. et mag. de zool. **4**:97, 1852.

7. Gervais, Paul: Memoire sur les formes cérébrales propres aux Carnivores vivants et fossiles, Nouv. arch. du Mus. d'hist. nat. de Paris **6**:103, 1870.

8. Meynert, T.: Die Windungen der convexen Oberfläche des Vorder-Hirnes bei Menschen, Affen und Raubthieren, Arch. f. Psychiat. **7**:257, 1877.

9. Mivart, St. George: Notes on the Cerebral Convolutions of the Carnivora, J. Linnean Soc. Zool. **19**:1, 1886.

Flesch,[10] Turner,[11] Fish [12] and Kappers,[13] have figured and given short descriptions of the brains of some of the other members of the Ursidae, including the polar bear (Ursus maritimus), the European brown bear (Ursus arctos) and the Malayan bear (Ursus malayanus).

The brain of the bear not only shows some interesting and important arrangements as regards the gyri and sulci of the cerebral hemispheres, but also represents an important stage in the evolution of that part of the cerebral cortex which in man is known as the island of Reil. Furthermore, in North America, Ursus americanus is the only member of the Ursidae which may be fairly easily procured for experimental study and which more or less readily lends itself to physiologic investigations on the central nervous system. Such a study of the motor area of the cerebral cortex, made by me in May, 1931, was briefly presented at a meeting of the American Association of Anatomists in March, 1932,[14] and will soon be published in detail. The brain of the bear used in the experimental study forms the basis for this paper,[15] in which an attempt will be made to present the interesting and important structural and evolutionary aspects of the cerebral hemispheres of the American black bear (Ursus americanus).

The American black bear is a representative of the arctoid group of the Carnivora, which besides the bears (Ursidae) includes the Procyonidae, a common representative of which is the raccoon, the Mustelidae, which includes such common and well known species as the otter, weasel, mink and skunk, and the Pinnipedia, including the seals, sea-lions and walruses. The brain of the bear not only exhibits those features which are characteristic of the brains of carnivores in general, but represents a phylogenetically higher type of development than is seen in some of the smaller members of the Carnivora, such as the cat

10. Flesch, Max: Versuch zur Ermittelung der Homologie der Fissura parietooccipitalis bei den Carnivoren, Fest-Schrift, Albert von Kölliker zur Feier seines siebenzigsten Geburtstages gewidmet von seinen Schülern, Leipzig, Wilhelm Engelmann, 1887.

11. Turner, W.: Comparison of the Convolutions of the Seals and Walrus with Those of the Carnivora and of Apes and Man, J. Anat. & Physiol. **22**:554, 1888; The Convolutions of the Brain; A Study in Comparative Anatomy, ibid. **25**:105, 1890.

12. Fish, P. A.: The Brain of the Fur-Seal, Callorhinus Ursinus; With a Comparative Description of Those of Zalophus Californianus, Phoca Vitulina, Ursus Americanus and Monachus Tropicalis, J. Comp. Neurol. **8**:57, 1898.

13. Kappers, C. U. A.: Die vergleichende Anatomie des Nervensystems der Wirbeltiere und des Menschen, Haarlem, de Erven F. Bohn, 1921.

14. Smith, W. K.: Anat. Rec. (supp.) **52**:35, 1932.

15. All the drawings of the bear's brain, with the exception of fig. 5, were made from the brain of the bear used for the study of the motor cortex. Figure 5 was made from a brain procured for me by Mr. Gerrit S. Miller, Jr., of the National Museum. Dr. James W. Papez also loaned me a specimen from the Cornell University laboratory.

(Felis domestica). In order, therefore, to make clear the morphology of the cerebral hemisphere of the bear and to understand clearly the phylogenetic changes which have occurred in the arrangement of the sulci and the gyri, it may be well to review briefly the condition as seen in the brain of the cat.

CEREBRAL HEMISPHERES IN FELIS DOMESTICA

In the brain of the cat (fig. 1), the sulci are clearly demarcated, but much branching or formation of secondary sulci is absent. Four rather simple gyri arch above a shallow sulcus which indicates the position of the sylvian fossa of higher forms. There is no sylvian fissure such as is seen in higher mammals, and therefore this shallow sulcus in the cat is probably best designated by the term pseudosylvian, as suggested by

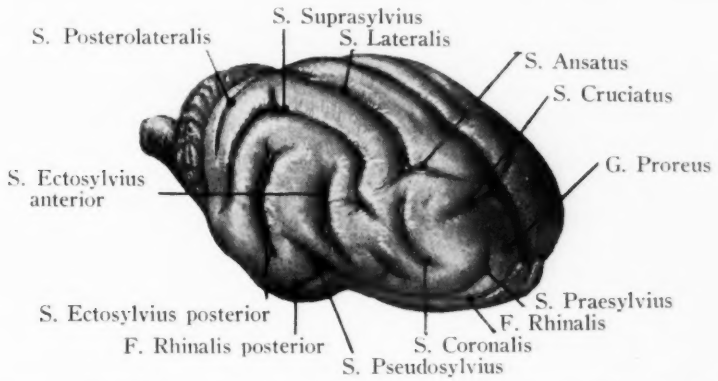

Fig. 1.—Anterolateral view of the right cerebral hemisphere of the cat (Felis domestica).

Elliot Smith.[16] Surrounding this sulcus is the sylvian gyrus, limited above and behind by the anterior and posterior ectosylvian sulci, which in the cat are not continuous with each other. This is in contrast to the condition seen in the Ursidae and in the Canidae, the group to which the dog belongs, for in these animals the ectosylvian sulcus forms a complete arch surrounding the sylvian gyrus. Above these can be seen the long, arched suprasylvian sulcus which separates the ectosylvian and suprasylvian gyri. These two gyri, as well as the corresponding sulci, may be separated into anterior, middle and posterior portions. In the cat the middle ectosylvian sulcus is not present.

The lateral gyrus is situated along the medial edge of the cerebral hemisphere, and is separated from the suprasylvian gyrus by the lateral sulcus, the anterior end of which bifurcates, thus producing the sulcus

16. Smith, G.: On the Homologies of the Cerebral Sulci, J. Anat. & Physiol. **36**:309, 1902.

ansatus. The lower branch of the sulcus ansatus sometimes continues directly into the coronal sulcus. The coronal sulcus is an important sulcus in the brain of carnivores, since many investigations by various workers show that it separates the motor areas of the anterior and posterior sigmoid gyri, which surround the cruciate sulcus, from inexcitable cerebral cortex. In the cat the cruciate sulcus extends on to the dorsomedial surface of the cerebral hemisphere and usually does not connect with any sulcus of the medial surface (fig. 2). The posterior lateral sulcus runs in a direction almost parallel to the occipital pole. Its upper end may be directly continuous with the posterior end of the lateral sulcus. However, it usually does not join the lateral sulcus, but terminates in the cortex more medial to it. Medial to the posterior lateral sulcus is the posterior lateral gyrus, which forms the cortex of the occipital pole on the medial border of the hemisphere.

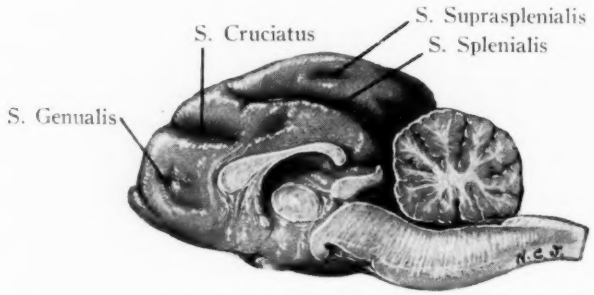

Fig. 2.—Midsagittal view of the brain of the cat, showing the gyri and sulci of the mesial surface.

The part of the olfactory brain made up of the olfactory bulbs, the olfactory tracts and the pyriform area is marked off from the rest of the cortex by the rhinal fissure. The rhinal fissure thus marks the boundary between the phylogenetically old olfactory cortex and the phylogenetically new cortex or neopallium. The rhinal fissure passes posteriorly on the lateral surface of the cerebral hemisphere and at its posterior end joins the pseudosylvian sulcus. An apparent continuation of the rhinal fissure constitutes the so-called postrhinal fissure, which separates the cortex of the temporal lobe from that of the pyriform area. In the cortex between the rhinal fissure and the coronal sulcus there is usually a short shallow sulcus, the sulcus diagonalis. In the specimen examined it did not join any other sulcus; but occasionally it may join the anterior ectosylvian. The presylvian or orbital sulcus lies in front of the coronal sulcus. It courses almost vertically downward for a short distance and then turns abruptly backward to join the rhinal fis-

sure. Around the upper end of the presylvian sulcus the anterior sigmoid gyrus passes abruptly forward into the gyrus proreus.

The gyri and sulci of the mesial surface of the hemisphere (fig. 2) present a very simple arrangement. The sulcus cruciatus cuts the dorsomesial border of the hemisphere and is prolonged on to the mesial surface in a posteroventral direction. It does not join any other sulcus. Lying inferior to the cruciate sulcus is a shallow sulcus, the genual. The cortex above the corpus callosum is furrowed by a rather long and deep splenial sulcus, above which may be seen a shallow depression, the suprasplenial sulcus.

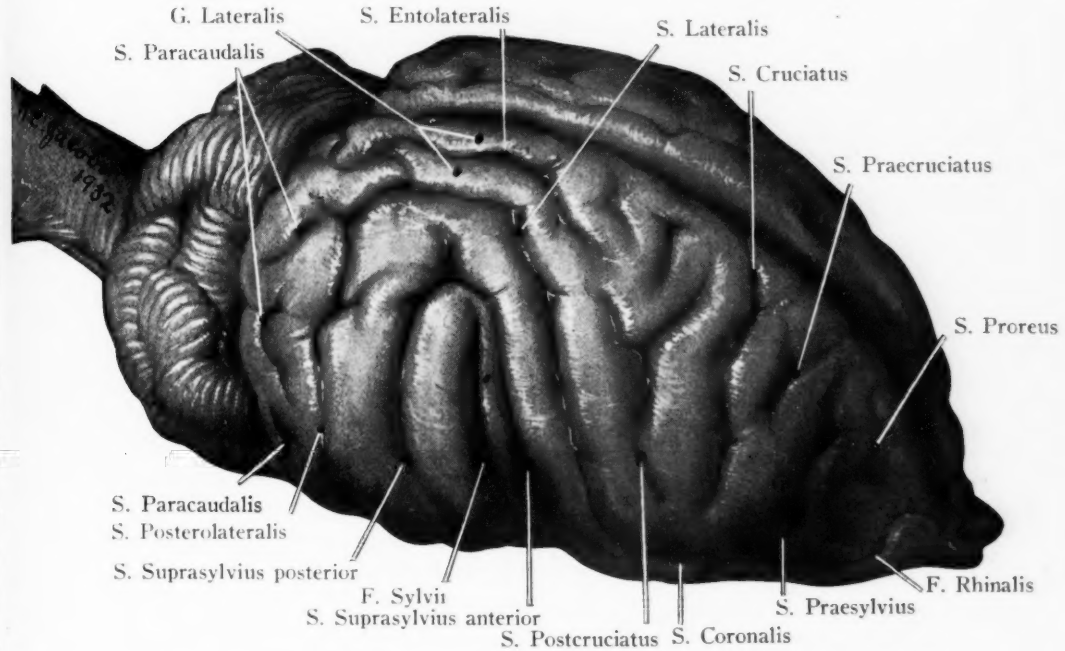

Fig. 3.—Anterolateral view of the right cerebral hemisphere of the bear (Ursus americanus).

CEREBRAL HEMISPHERES IN URSUS AMERICANUS

The simple arrangement of the gyri and sulci seen in the cat is in striking contrast to that seen in the bear. In the bear (fig. 3) only three arcuate gyri are seen on the surface of the cerebral hemisphere, in contrast to the four seen in the cat. In the brain of the bear the gyri are not so simple, but present a more convoluted appearance and are more frequently divided by secondary sulci. The lateral gyrus of the bear's brain shows this to a pronounced degree. This gyrus exhibits a strong tendency to double, especially in its posterior part, where the

entolateral sulcus appears in it. In addition, the pseudosylvian fissure with its surrounding sylvian gyrus (gyrus arcuatus primus), which is so clearly seen on the lateral surface of the cat's brain (fig. 1), in the bear has sunk into the brain so that a true sylvian fossa exists. There is thus produced a long and deep sylvian fissure into the depths of which the sylvian gyrus (gyrus arcuatus primus) and the anterior and posterior ectosylvian sulci have disappeared. The anterior and posterior ectosylvian gyri constituting the second arcuate gyrus form the lips of the fissure.

If one opens the sylvian fissure and looks into its depths (fig. 4), one finds the sylvian gyrus surrounding the pseudosylvian sulcus. The

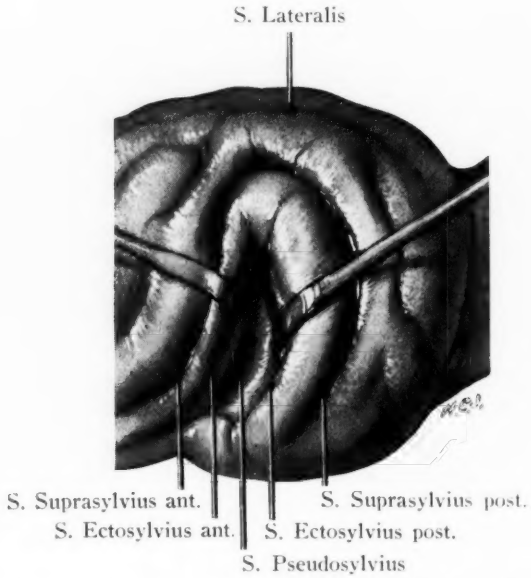

Fig. 4.—Lateral view of the left cerebral hemisphere of the bear (Ursus americanus), showing the sylvian gyrus at the bottom of the sylvian fossa.

anterior portion is more slender than the posterior portion, but is greater in extent, for whereas the posterior portion passes down and fuses with the lobus pyriformis, the anterior portion passes forward under cover of the gyrus ectosylvius anterior and fuses with the presylvian gyrus just above the rhinal fissure. The anterior ectosylvian sulcus continues forward directly into the presylvian sulcus; the posterior ectosylvian sulcus, covered over by the cortex of the posterior ectosylvian gyrus, ends on reaching the pyriform lobe. It is not directly continuous with the posterior rhinal fissure. In the bear, not only have the sylvian gyrus and the anterior and posterior ectosylvian sulci sunk

into the brain, thus disappearing from the lateral cerebral surface, but the ectosylvian gyri, especially the anterior one, exhibit a pronounced tendency to sink in also. Occasionally a more advanced stage is seen in which the top of the anterior ectosylvian gyrus has completely disappeared beneath the cortical surface. Such an instance is seen in figure 5, which is a drawing made from the brain loaned me by Mr. Gerrit S. Miller, Jr. In this case, the sylvian fissure becomes longer than usual, and the top of it presents a true processus acuminis. The sinking in of the sylvian gyrus and the tendency of the ectosylvian gyri to sink in also are of great importance phylogenetically, because this sinking undoubt-

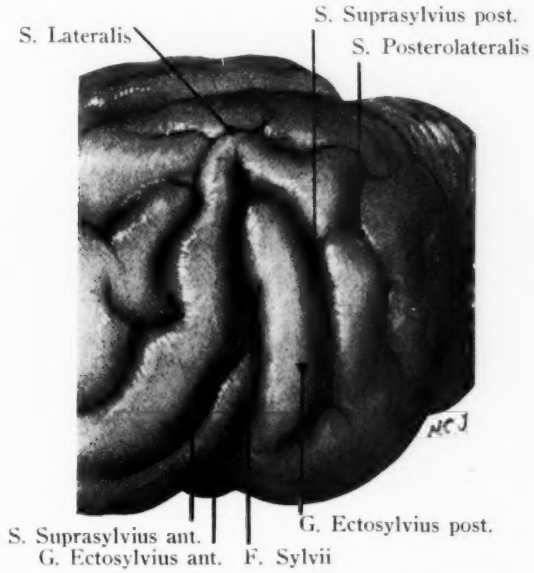

Fig. 5.—Lateral view of the right cerebral hemisphere of the bear (Ursus americanus), showing the disappearance of the upper part of the anterior ectosylvian gyrus into the sylvian fossa.

edly represents an important stage in the beginning of the formation of that part of the brain which in higher mammals is known as the insula or the island of Reil. In the ungulates the cortex surrounding the pseudosylvian sulcus has already sunk into the brain and become covered over by the adjacent cortex. The condition as seen in the bear represents a simpler development, and it is in the bears, therefore, that the beginning of the formation of the island of Reil can best be studied.

Just above the ectosylvian gyri is the suprasylvian sulcus, and above this are situated the large anterior, medial and posterior suprasylvian gyri (fig. 3). The suprasylvian gyri are well developed in Carnivora in general, and in the bear exhibit their usual carnivore characteristics.

According to Elliot Smith,[16] the suprasylvian sulcus is the most stable sulcus on the lateral aspect of the cerebral hemisphere.

Surrounding the suprasylvian gyri is the lateral sulcus. In the bear its anterior end usually joins the coronal sulcus. Occasionally, however, the two do not unite. The bifurcated anterior end of the lateral sulcus known as the sulcus ansatus, which is so clearly seen in the cat (fig. 1), has been taken into the union of the lateral and coronal sulci, and hence no ansate sulcus is present. This is not always the case, as Kappers [13] stated that in bears an ansate sulcus may sometimes be present and may unite with the coronal sulcus.

The condition seen in figure 3 differs from that which has been described by various writers as typical of carnivores as, for example, the raccoon, in which the lateral sulcus does not join the coronal sulcus, and therefore a distinct ansate sulcus is present. The posterolateral sulcus on the right side of the specimen shown in figure 3 is directly continuous with the lateral sulcus. On the left side the two do not join, and the left posterolateral sulcus is not as well developed as the right. Between the posterolateral sulcus and the caudal edge of the cerebral hemisphere is the large vertical posterolateral gyrus, which is complicated by three small vertical sulci, designated by Elliot Smith [3] as the paracaudal sulci.

In the frontal region of the neopallium one finds the two sulci, the presylvian and the coronal, which Kappers [13] pointed out occur with great constancy in lower mammals. Both are well developed on the two sides of the brain. The presylvian sulcus, which makes its appearance in the marsupials, is quite distinct in the bear. It is deep and is apparently connected with the rhinal fissure, a condition which is the rule in carnivores; in the ungulates it is usually separate. Just anterior to the presylvian sulcus is the sulcus proreus, which in this case is not connected to the presylvian sulcus. Kappers [13] described and illustrated such a connection in Ursus malayanus.

The coronal sulcus is a conspicuous sulcus in the bear. Dorsally it connects with the anterior end of the lateral sulcus in a manner which Kappers [13] concluded is common to all bears and which is also seen in the Mustelidae. This is in contrast to the condition in some Felidae and Canidae, e. g., the lion and the hyena, in which it remains unconnected. In the bear the coronal sulcus has been displaced downward owing to the great development of the cruciate sulcus and the sigmoid gyri. It thus comes to occupy a position very near the ventral surface of the brain. Compared with the cat, the bear has the cruciate sulcus and the coronal sulcus displaced caudally, so that the region of the frontal lobe is increased materially in size.

The cruciate sulcus, a distinctive carnivore attribute, first called cruciate by Leuret,[5] is well developed in the bear. It is quite long, measuring about 4 cm., and quite deep. It runs in a slightly oblique direction from above, down and forward. A characteristic of this sulcus in all carnivores is that it usually does not branch and does not connect with any other sulcus. It cuts the dorsomedial border of the hemisphere and is continued for a distance of about 1 cm. on to the medial surface of the brain, running posteriorly (fig. 6), but does not connect with any sulcus of the mesial surface. In front and behind the cruciate sulcus are two gyri, the anterior and posterior sigmoid gyri. These unite around the lower end of the cruciate sulcus. It is important

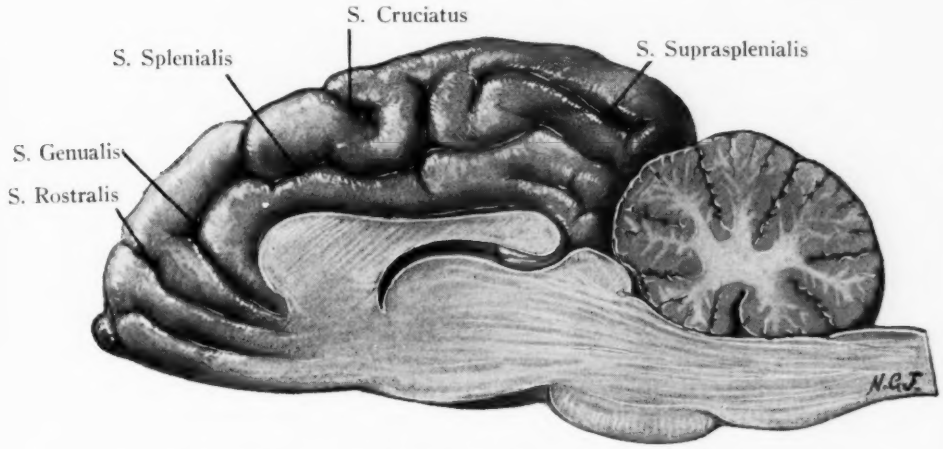

Fig. 6.—Midsagittal view of the brain of the bear (Ursus americanus), showing the gyri and sulci of the mesial surface.

to note that in the bear these gyri have increased considerably in size as compared with those of the cat.

In front of the cruciate sulcus there is a shallow sulcus called the precruciate from its position. The relation of this sulcus to the cruciate sulcus is such that a triangular gyrus is enclosed between the two. This gyrus, first described by Gervais[7] and named by him the lozenge area, has been called by Mivart[9] the ursine lozenge. This area of the cortex was thought by Mivart to be of great importance in establishing a phylogenetic relationship between the Pinnipedia and the Ursidae; however, it has been described as being present in other members of the Arctoidae and is not peculiar to bears. It therefore is probably best designated as the arctoid lozenge. Since the precruciate sulcus neither extends on to the mesial surface of the hemisphere nor joins the cruciate sulcus, laterally the boundaries of the ursine lozenge are not complete. In the cortex behind the cruciate sulcus may be seen the postcruciate

sulcus, which marks the posterior boundary of the posterior sigmoid gyrus.

The olfactory tracts of the bear are well developed (figs. 3 and 7). Anteriorly they terminate in fairly large olfactory bulbs, which project up in front of the anterior part of the brain and are only partly shown in the drawing. Posteriorly they terminate in the extensive olfactory cortex. The degree of development of the olfactory apparatus in Ursus americanus is similar to that exhibited by all other Ursidae, a degree which accords well with the fact that bears depend largely on their olfactory sense for food and to apprise them of danger. They are truly macrosmatic mammals. The olfactory fissure is completely hidden by the olfactory crus and bulb; when these are removed, this shallow fissure is seen.

The rhinal fissure forms the lateral boundary of the olfactory tract. It passes in a caudolateral direction to the sylvian fissure. The considerable development of the neopallium in the bear has pushed the rhinal fissure ventrad so that it has come to lie almost entirely on the ventral surface of the brain. From the sylvian fissure there passes backward a short fissure which is an apparent continuation of the rhinal fissure. It is known as the postrhinal fissure. If one examines this fissure carefully, it will be seen that it does not connect with the rhinal fissure but passes into the sylvian fossa and there is directly continuous with the posterior ectosylvian sulcus, which lies buried in the caudal wall of the sylvian fossa (fig. 4).

It is well known that the system of sulci and gyri on the mesial surface of the cerebral hemispheres of the carnivores represents an intermediate or transitional stage between the ungulates and the primates. On the anterior mesial surface of the brain of the bear (fig. 6) a distinct sulcus rostralis and genualis may be seen. Behind the genualis is the sulcus splenialis, which in carnivores usually does not connect with the genualis. In the brain shown, however, such a connection exists, and the resulting sulcus resembles the callosomarginal sulcus of primates. In addition, the splenialis is connected at its posterior extremity with the retrosplenial or calcarine sulcus. The sulcus splenialis is a very deep sulcus. Below it lies the gyrus cinguli (gyrus fornicatus). Above it lies the gyrus splenialis. In some carnivores the anterior part of the sulcus splenialis may anastomose with the sulcus cruciatus, but according to Kappers [13] such an anastomosis does not occur in any of the bears. The specimens studied in connection with this paper confirm Kappers' findings. The sulcus cruciatus, although extending on to the mesial surface, does not connect with any other sulcus. In the middle part of the sulcus splenialis there is seen a distinct dorsal coursing ramus, the ramus ascendens medius splenialis or sulcus verticalis, which various investigators have described as occurring in the brain of both

carnivores and ungulates. Above the posterior part of the splenial sulcus, and running parallel to it, there is a fairly deep sulcus known as the suprasplenial.

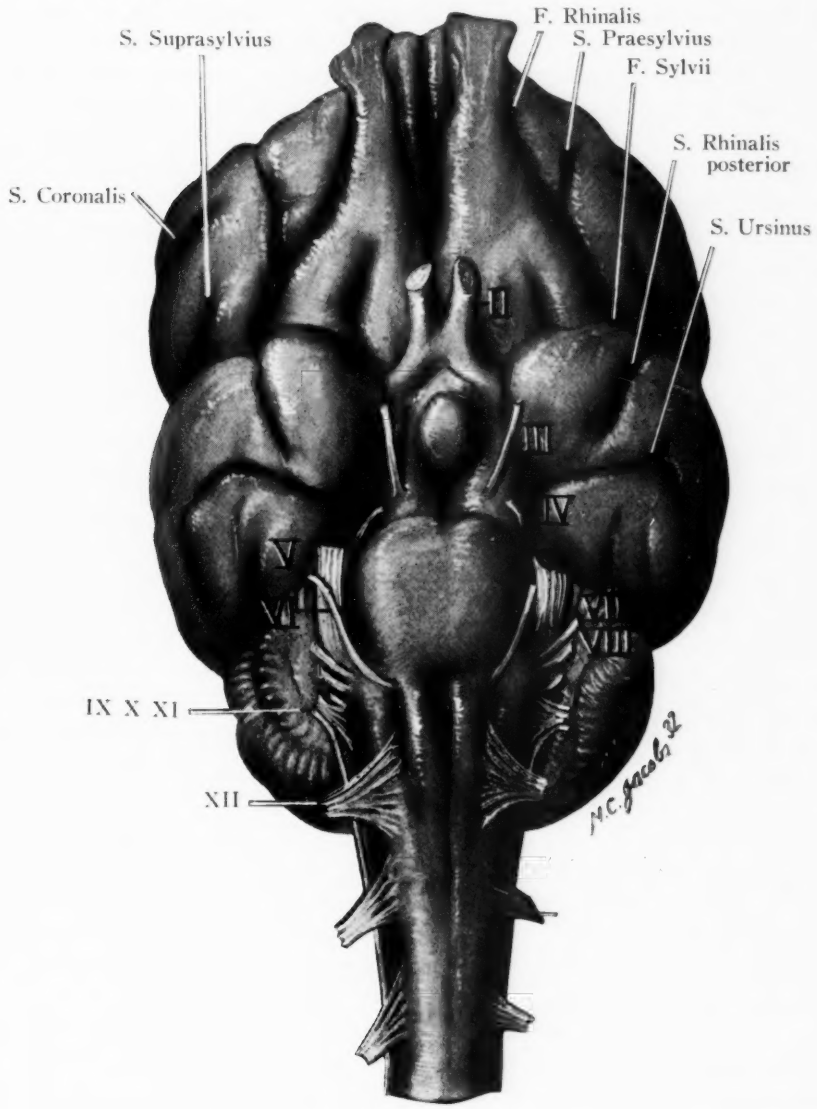

Fig. 7.—Ventral view of the brain of the bear (Ursus americanus). The numbers indicate the cranial nerves.

The retrosplenial or calcarine sulcus is seen to be directly continuous with the sulcus splenialis (figs. 6, 7 and 8). This differs from the brain of Ursus malayanus illustrated by Kappers,[13] in which the retrosplenial

part of the sulcus splenialis is separate. The calcarine sulcus is quite deep and joins the splenial sulcus at an acute angle. Near its junction with the splenial sulcus the calcarine sulcus gives off a short but very deep sulcus which probably corresponds to the posterior calcarine of higher mammals. If the lips of the calcarine sulcus are separated at this junction, there will be seen on the superior and inferior walls three or four gyri and sulci placed almost at right angles to the sulcus. In a recent study by Cohn and Papez [17] on the occurrence of the posterior calcarine sulcus in the dog, this sulcus, surrounded by visual cortex, was found to be well developed in 64 per cent of the brains examined, and was entirely absent in only 15 per cent. In the bear, therefore, one would expect to find it in all or nearly all cases. It was present in the

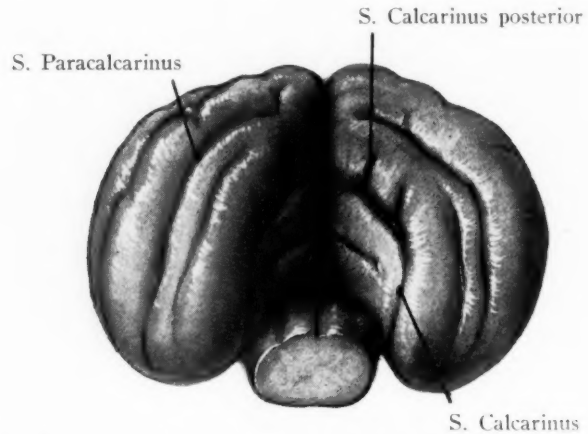

Fig. 8.—Posterior view of the cerebral hemispheres of the bear (Ursus americanus), showing the arrangement of the gyri and sulci.

four specimens used in this study. The most lateral sulcus on the occipital pole of the brain has been designated the paracalcarine by Elliot Smith.[3] This sulcus and a shorter one lying just medial to it have been called the occipitotemporalis primitivus by Kappers.[13] Both sulci are nearly parallel to the sulcus calcarinus and run in an almost vertical direction on the occipital surface.

The calcarine sulcus is directly continuous with a sulcus that runs lateral and slightly forward on the ventral surface of the brain behind the caudal end of the posterior rhinal fissure (fig. 7). From a study of many mammalian brains, Elliot Smith [3] came to the conclusion that in its fully developed form this sulcus is peculiar to brains of bears, and hence he designated it as the ursine sulcus.

17. Cohn, H. A., and Papez, J. W.: The Posterior Calcarine Fissure in the Dog, J. Comp. Neurol., to be published.

SUMMARY

The brain of the bear, therefore, presents morphologic features which stamp it as being a phylogenetically higher type of brain than that seen in the Felidae and Canidae. In addition, it presents features typical of the brains of the arctoid carnivores, i. e., a long sylvian fissure surrounded by acutely flexed ectosylvian gyri, the anterior one of which exhibits a pronounced tendency to disappear beneath the cortical surface. The sylvian gyrus and the ectosylvian sulci, which are so clearly seen on the lateral surface of the cat's brain, have disappeared beneath the cortical surface. This represents a simple stage in the development of that part of the cortex which in man is known as the island of Reil.

The lateral gyrus is remarkable for its great depth, and it has become partially subdivided by an entolateral sulcus. The cruciate sulcus is long and deep, and although it extends on to the mesial surface of the hemisphere it does not join any other sulcus. The presence of a precruciate sulcus results in the formation of a well defined arctoid lozenge, the boundaries of which are not complete. This area of the cortex probably represents the first appearance on the dorsal surface of the brain of the cortex which is destined to form the superior frontal gyrus. The great extent of the cortex of the anterior and posterior sigmoid gyri and the adjacent cortical fields is most likely correlated with the gyri and the adjacent cortical fields is most likely correlated with the great use which the bear makes of the extremities, the anterior extremity being capable of being used in a very dexterous manner. This greater differentiation of movements in the extremities, especially in the foreleg and paw, has resulted in a greater development of the motor, sensory and association areas corresponding to the foreleg and the hindleg. Therefore, it is not surprising to find that the frontal lobe of the brain shows a great increase in size in comparison to its extent in the Felidae.

MOTOR CORTEX OF THE BEAR (URSUS AMERICANUS)

A PHYSIOLOGIC AND HISTOLOGIC STUDY

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Before 1870, the doctrine that the cerebral cortex was inexcitable to artificial stimulation was generally held by investigators. As early as 1756, Haller [1] reported a series of experiments performed six years before on dogs, cats and goats by his pupil Zinn, in which he was unable to produce muscular movements by mechanical or chemical irritation applied to the cerebral cortex. Later investigators, including Magendie,[2] Longet,[3] Budge [4] and Matteucci,[5] were also unable to produce movements by various methods of artificial stimulation, including the use of the galvanic current.

On the basis of such results reported by the leading experimentalists of their time, it is not surprising to find that investigators generally agreed that muscular movements could not be obtained on irritation of the cerebral cortex. In addition to denying the possibility of artificial excitation of this part of the central nervous system, it was almost universally held that no localization of function existed; that the cerebral cortex functioned as a whole, and that any particular loss of function depended not on the removal of any particular area but on the extent of the lesion, i. e., on the amount or the mass of the cortex destroyed. One of the most zealous advocates of the theory of the inexcitability of the cerebral cortex and of the doctrine of mass action was the distinguished French physiologist, Flourens.[6] The doctrine of mass action

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2. Magendie, François: Leçons sur les fonctions et les maladies du système nerveux, Paris, 1839.

3. Longet, F. A.: Anatomie et physiologie du système nerveux de l'homme et des animaux vertébrés, Paris, Masson & Cie, 1842.

4. Budge, Julius: Untersuchungen über das Nervensystem, Frankfort, Jager, 1842.

5. Matteucci, Carlo: Traité des phénomènes électrophysiologiques des animaux, Paris, Fortin, Masson & Cie, 1844.

6. Flourens, P.: Recherches expérimentales sur les propriétés et les fonctions du système nerveux, ed. 1, Paris, Crevot, 1824; ed. 2, Paris, J.-B. Baillière, 1842.

in the cerebral cortex as held by Flourens and his followers is best summarized in Flourens' own expression: "Dés qu'une perception est perdue, toutes le sont, dés qu'une faculté disparaît, toutes disparaissent." (When one perception is lost, all are lost; when one faculty disappears, all disappear.)

In contrast to this view, the school of phrenology, led by Gall and his pupil Spurzheim,[7] believed in a strict localization of function in the cerebral cortex. The exaggerated claims of the phrenologists and the fact that these claims could not be confirmed by experiment soon brought phrenology into disrepute.

Bouillaud [8] brought forth some rather convincing evidence in favor of the theory of the localization of cerebral function. From a careful study of a series of patients with disorders of speech, he came to the conclusion that the frontal lobe contained the center for the production of articulate speech. The many investigations and critical analyses carried out by Bouillaud and many other workers culminated in the work of Broca,[9] who showed in a convincing manner that the cerebral cortex in the region of the posterior part of the second and third left inferior frontal gyri was intimately associated with the production of articulate speech. In addition, the writings of Hughlings Jackson [10] on epilepsy had begun to throw doubt on the doctrine of the action of the cerebral cortex as a whole, and seemed to point the way to the theory of cortical localization.

With such conflicting views dominating the field of cerebral physiology, it was only natural that the discovery of the electrical excitability of certain areas of the cerebral cortex of the dog by Fritsch and Hitzig [11] in 1870 should give a tremendous impetus to investigations on the problem of cerebral localization and on the function of the cerebral cortex. Not only did their results disprove the theory of the inexcitability of the cerebral cortex to artificial stimulation, but their results gave evidence in favor of the localization of function. In addition, their investigations marked the beginning of a new era in cerebral physiology, for they had introduced a new method of investigation which when

7. Gall, F. J., and Spurzheim, J. G.: Anatomie et physiologie du système nerveux en general, et du cerveau en particulier, Paris, F. Schoell, 1810-1819.

8. Bouillaud, J.: Recherches cliniques propres à démontrer que la perte de la parole correspond à la lésion des lobules antérieurs du cerveau, Arch. gén. de méd. **8**:25, 1825.

9. Broca, P.: Remarques sur le siège de la faculté du langage articulé, suivies d'une observation d'aphémie (perte de la parole), Bull. Soc. anat. de Paris **6**:330, 1861; Nouvelle observation d'aphémie produite par une lésion de la moitié postérieure des deuxième et troisième circonvolutions frontales, ibid. **6**:398, 1861.

10. Jackson, Hughlings: A Study of Convulsions, St. Andrews M. Grad. A. Tr. **3**:162, 1870.

11. Fritsch, G., and Hitzig, E.: Ueber die elektrische Erregbarkeit des Grosshirns, Arch. f. Physiol., 1870, p. 300.

applied to the brain of the living animal evoked responses that could be directly observed and recorded.

At first investigators confined their efforts to determining the position and extent of the responsive areas and to recording in writing the movements obtained. Many investigations were also carried out in order to determine the effect of the removal of all or a part of this area. With the development of the histologic study of the cerebral cortex, it was found that the cortex of the electrically responsive areas possessed a cell lamination which differed from that of other cortical regions.

In spite of the large amount of work which has been done on the electrically responsive areas, their function is not as yet known. It is not known whether movements normally arise in the cerebral cortex or are initiated in subcortical centers and then rearranged in the motor areas. Neither is the function of the cell layers known. In addition, great disagreement exists among investigators as to the exact movement which may be elicited from any specific area. Such disagreement among experimental neurologists of equal ability is probably largely due to the lack of an accurate method of recording the movements obtained. It is believed that this difficulty can be entirely overcome by the use of motion pictures, for by this method not only can the exact movement elicited from stimulation of any point be accurately recorded, but a permanent record is secured which can be repeatedly studied for analysis of the movements obtained from any area, and for a comparison of the movements obtained from one animal with those of another.

Among the carnivores the species most frequently studied have been the cat and the dog. Studies by electrical stimulation of carnivores such as the bear, the brain of which from an anatomic point of view shows a higher state of development than the brain of the cat or the dog, are entirely lacking. This investigation is an attempt to make a combined physiologic and histologic study of the electrically responsive areas in the cerebral cortex of the black bear (Ursus americanus). The majority of the movements elicited from stimulation of the left cerebral cortex have been recorded by motion pictures.

EXPERIMENTAL PROCEDURE

Electrical stimulation of the cerebral cortex was carried out on two male bears, each weighing approximately 75 Kg. The first experiment was performed on May 5, 1931, on a male bear 14 months old, and the results herein described together with their cinematographic record were made then. The study of a second bear procured later in order to check the results from the first added nothing new, but in general corroborated the original findings. Venous abnormalities over the motor cortex of the second bear, together with the development of a tremor which could not be controlled, prevented satisfactory photographing of

the movements obtained in the extremities. Nevertheless, in spite of these difficulties, the extent of the motor areas and the movements obtained from them were apparently the same in the two animals.

The administration of 1.5 Gm. of sodium amytal by mouth two hours before the experiment was begun served only to make the animal slightly drowsy. Anesthesia was then produced by ether until complete relaxation of the muscles had occurred and it was certain that the bear could not make any voluntary movement. The animal was then placed astride a supporting frame especially constructed so that all four extremities would hang perfectly free, and the head would be properly supported. During the experiment, anesthesia was maintained by means of ether administered by the cone method.

During the entire procedure normal body temperature was maintained by means of electric lamps suitably placed. Bleeding was carefully controlled so that the amount of blood lost was very small. A fall in the blood pressure with the resultant impairment of the circulation in the cerebral cortex and the subsequent loss of excitability was thus entirely avoided.

A midline skin incision was made over the skull so as to give plenty of space for exposing the entire cerebral hemisphere on the left side. The left temporal muscle, powerfully developed, was cut near its attachment to the cranial vault and removed from the bone by means of a periosteal elevator. The zygomatic arch was next removed and the temporal muscle strongly retracted, thus affording ample space for determining the lowermost limits of the electrically responsive area.

The skull was next trephined over a point which would be certain not to be over the motor cortex. The dura was separated from the overlying bone for a short distance beneath, and the bone over the separated area was removed with rongeurs. This process was repeated until the entire left cerebral hemisphere was exposed. Bleeding from the bone was at all times controlled by the application of bone wax, and the dura and surrounding tissues were kept moist and warm by the constant application of Ringer's solution heated to 37 C. Great care was taken to avoid pressure on the brain, and in order to avoid chilling the cortex the instruments used were heated to body temperature on a slide warming table. When the skull had been removed as far as the superior longitudinal sinus above and the base of the skull below, and when the entire cerebral hemisphere including the olfactory lobe had been exposed, the dura was lifted up by means of a dural hook and incised. This was followed by the escape of a moderate amount of clear cerebrospinal fluid, indicating the absence of subdural hemorrhage. The dura was then incised longitudinally and transversely and reflected, thus exposing the cortex, which was of excellent color and showed no evidence of injury. The constant application of warm Ringer's solution protected the exposed cortex from the injurious effects of drying and cooling.

The administration of the anesthetic was controlled so as to produce an anesthesia of a degree that would just abolish voluntary movements in the animal, as it is well known that an anesthesia of too great a depth will so depress the cortex as to render it unresponsive to electrical stimulation.

Faradic current from a Du Bois-Reymond inductorium connected to one dry cell battery was used. A fairly weak current, the distance of the secondary coil from the primary coil being about 9 cm., was sufficient to elicit a response. In order to prevent spread of the current to adjacent areas, cotton pledgets were used to absorb the excess moisture from each area immediately before stimulation. During the experiment the same area was stimulated many times with both bipolar and unipolar electrodes. In this experiment the use of the unipolar electrode appeared to possess no advantage over the use of the bipolar electrode. Between

stimulations the cortex was covered with warm, moist compresses so that its normal excitability would be maintained at a maximum. It is well known that continued successive stimulations of any point on the motor cortex result in a gradual loss of excitability. Under the influence of warm, moist compresses the excitability always recovers after one or two minutes, unless the area has been injured.

The entire exposed cerebral cortex was subjected to electrical stimulation. The exact area stimulated was recorded by making a sketch of the brain with its surrounding blood vessels and then plotting in the motor areas as outlined during the experiment. At the end of the experiment and before the animal was killed, fixing solution was poured over the surface of the brain in order to fix the cortex and the blood within the vessels (fig. 1); thus a permanent picture of the blood

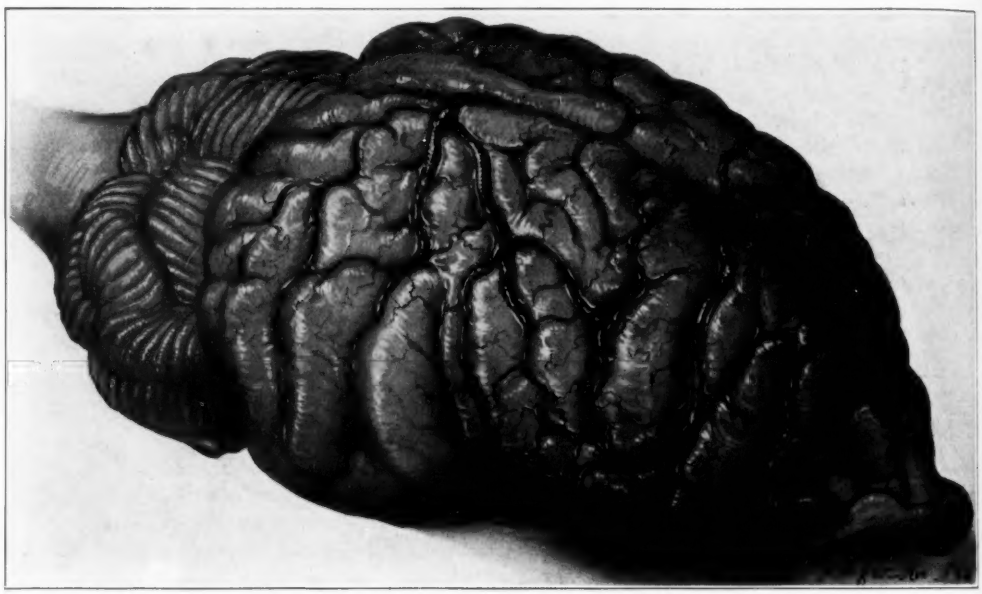

Fig. 1.—Anterolateral view of the right cerebral hemisphere of the bear (Ursus americanus), showing the arrangement of the veins, gyri and sulci.

vessels was made, and on comparison with the drawing made during the experiment the exact position and extent of the area stimulated could be easily identified. The left cortex was first stimulated, and the movement obtained from the different areas were recorded by means of motion pictures. Later the right cortex was explored with the same results. No photographs were made of the movements elicited from stimulation of the right side of the brain.

RESULTS

On reflecting the dura, the long cruciate sulcus containing a large vein and surrounded by the anterior and posterior sigmoid gyri could be easily identified. The entire exposed cortical field, limited above by the medial edge of the cerebral hemisphere, below by the rhinal and post-

rhinal fissures, anteriorly by the olfactory lobe, and posteriorly by the posterosuperior edge of the cerebral hemisphere, was subjected to electrical stimulation. It is well known that in the common carnivores, such as the dog and the cat, the motor cortex is situated in close proximity to the cruciate sulcus. Therefore, in order to determine whether the cortex was excitable this region of the exposed brain was stimulated first. Stimulation of the cortex of the posterior sigmoid gyrus with a weak faradic current elicited responses in the extremities. Stimulation of the entire exposed cerebral cortex evoked no response except in the cortex of the posterior sigmoid gyrus and the cortex surrounding the lower or lateral end of the cruciate sulcus. The wedge-shaped gyrus known as the arctoid lozenge, which is situated anterior to the upper part of the cruciate sulcus, proved to be inexcitable.

It having been thus ascertained that the motor area was limited to the cortex in the vicinity of the cruciate sulcus, a general survey of this region was made first. This was followed by a systematic analysis of the areas yielding different responses. The movements elicited from the different areas were recorded in writing and by means of motion pictures, and the extent of the region from which the various movements were obtained was plotted on the sketch of the brain which had been made before stimulation was begun. Usually the movements were elicited most easily and were most pronounced when one applied the electrode near the cruciate sulcus. As one receded from the sulcus, a point was arrived at from which the movement could no longer be elicited. This place was taken as the limit of the motor cortex and accordingly plotted on the drawing (fig. 2). The different areas are not sharply demarcated from each other, but overlap to a slight extent. Stimulation of this junctional zone usually evoked responses in each of the adjoining areas.

The cortical areas (fig. 2 *A* and *B*) from which movements of the hindleg were elicited were found to be situated in the uppermost part of the posterior sigmoid gyrus and, as shown in the drawing, this area reaches the medial border of the cerebral hemisphere. At the conclusion of the experiment, attempts were made to stimulate the cortex of the medial surface in order to determine whether or not the motor cortex passed on to this part of the brain. This procedure necessitated ligation of the veins which empty into the longitudinal sinus at this point. Although no movements were obtained on electrical stimulation, one cannot conclude from this that the motor cortex in the bear does not extend on to the medial surface, because it is possible that owing to the ligation of the veins draining this area the circulation was interfered with to such an extent as to render the cortex of this part inexcitable. Over the greater part of the hindleg area the complex movement obtained consisted of extension at the ankle joint with flexion at the knee and hip joints on the

contralateral side (fig. 3). At the same time a slight external rotation occurred. This movement was similar to that which the animal makes when it raises the foot and flexes the leg in order to advance it in the act of walking. Simultaneously there occurred an ipsilateral movement consisting of flexion at the ankle joint and extreme extension at the knee and hip joints. This movement was not photographed. Careful analysis of these movements discloses the fact that, although not identical in every detail, they are fundamentally the movements which the animal executes while walking; i. e., with every advance (chiefly flexion) of the

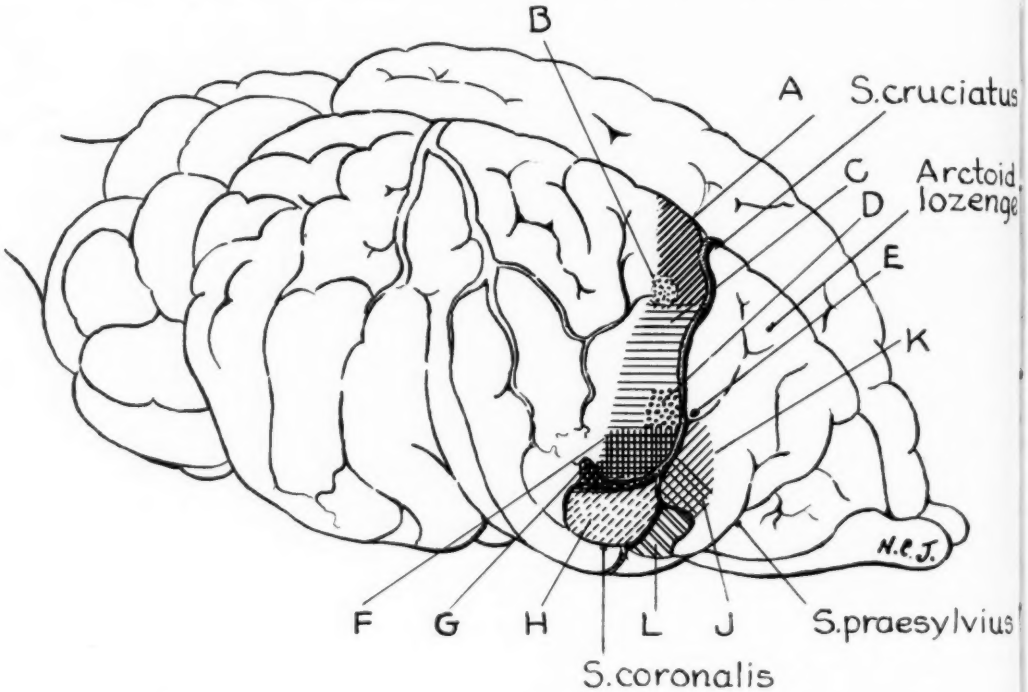

Fig. 2.—Outline drawing of the right cerebral hemisphere, showing the position and extent of the motor areas: *A* and *B*, hindleg; *C*, *D*, *E* and *F*, foreleg; *G*, neck and shoulder; *H*, facial-masticatory; *J* and *K*, face; *L*, face, tongue and larynx.

contralateral hindleg there is a simultaneous regression (chiefly extension) of the ipsilateral hindleg.

When the bilateral movement just described was elicited from stimulation near the anterior edge of the hindleg area, it was occasionally accompanied or followed by a contraction of the hyperaxial musculature of the trunk, thus producing an arching of the spine in the lumbar region. At the same time flexion of the tail was observed.

In the hindleg area only one region responded with extension movements of the contralateral hindleg (fig. 2 *B*). This region was situated near the inferior boundary of the posterior part of the hindleg area. Stimulation of this area always evoked extension of the contralateral hindleg.

If one examines carefully the motion pictures showing the flexion movement of the contralateral hindleg (fig. 3), it will be seen that during the contraction of the muscles of the hindleg the foreleg undergoes a slight straightening. This may be due to an increase in tonus in the muscles of the foreleg, or it may be entirely passive, owing to a shift in the axis of the body of the animal during the bilateral movements of the hindleg. The correct explanation of this phenomenon cannot be ascertained from this study.

The cortical region from which movements of the foreleg were elicited was found to be situated behind the cruciate sulcus lateral to the hindleg area (fig. 2 *C*, *D*, *E* and *F*). This region gave a contralateral response only. As may be seen from the drawing, the motor cortex of the foreleg on the lateral surface of the brain was found to occupy an area much larger than that of the motor cortex of the hindleg. In the upper or more medial part of the foreleg area (fig. 2 *C*) stimulation evoked a movement consisting of flexion at the wrist and elbow (fig. 4). This movement was of a rather simple type and resembled the contralateral flexion movement elicited from the hindleg area. An area of cortex (fig. 2 *D*) lying just behind the cruciate sulcus opposite the lower end of the arctoid lozenge responded by supination of the foreleg followed by slight flexion at the wrist (fig. 5). Just across the cruciate sulcus at a point (fig. 2 *E*) at the tip of the arctoid lozenge, stimulation produced exactly the same movement. Because of the proximity of the blood vessels to the point stimulated, it may be that the stimulus spread to the motor cells in the anterior wall of the cruciate sulcus, since histologic examination discloses the fact that the cortex of the arctoid lozenge which is exposed on the cerebral surface is nonmotor in type, even up to its utmost lateral tip. Histologically, the motor cortex in the anterior wall of the cruciate sulcus at this point almost reaches the lateral cerebral surface.

In contrast to the rather simple movements of the foreleg just described, a quite complicated movement was obtained from the more lateral part of the foreleg area (fig. 2 *F*). Electrical stimulation of this area produced a complex contralateral response consisting of a slight extension of the paw at the wrist, followed by flexion at the wrist with a simultaneous supination of the paw and forearm with flexion at the elbow and extension at the shoulder (fig. 6). This movement was elicited many times and was generally more pronounced than is shown in the photographs. Very often it almost exactly duplicated the move-

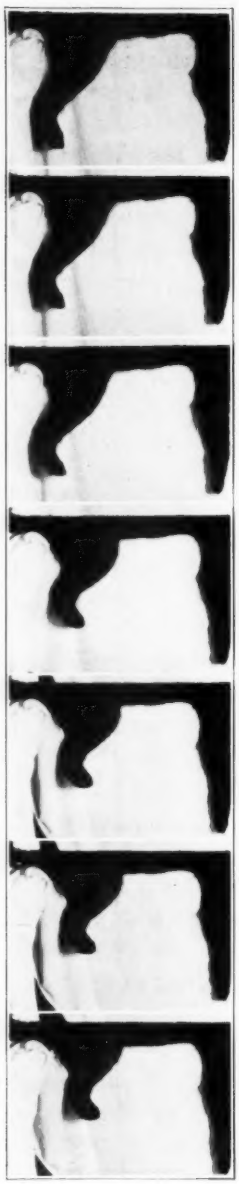

Fig. 3

Fig. 4

Fig. 5

Fig. 3.—The contralateral movement of the hindleg elicited from area *A* (fig. 2).

Fig. 4.—The movement elicited from area *C* (fig. 2). Flexion of the contralateral foreleg at the wrist and elbow.

Fig. 5.—The movement elicited from areas *D* and *E* (fig. 2). Supination of the contralateral foreleg with slight flexion at the wrist.

ment which the bear executes when a small piece of food is reached for, picked up, held in the palm of the paw and brought to the mouth. In this movement, as in all other complex muscular movements elicited from the cortex, a brief application of the electrodes produced the initial components; a more prolonged application produced the entire complex movement.

Situated just below and slightly posterior to the foreleg area, and for the most part enclosed between two veins draining into the large cruciate vein, an area was found (fig. 2 *G*) which on stimulation gave rise to a movement that was exclusively contralateral. This movement consisted of elevation of the shoulder, accompanied by a turning of the head to the contralateral side and at the same time flexion of the head toward the shoulder. The act of turning the head to the contralateral side may be seen in figure 7, and is evident from the fact that in the last picture the tip of the nose is closer to the left hand edge than in the first one. As may also be seen, this movement was usually accompanied by a slight contraction of some of the facial muscles, thus producing an elevation of the upper lip with a greater disclosure of the teeth. This movement, apart from that in the facial muscles, was evidently caused by a coordinated contraction of those muscles supplied wholly or in part by the spinal accessory nerve.

On stimulation of the various areas in the cortex surrounding the lower end of the cruciate sulcus, movements of the facial and masticatory muscles, of the larynx and of the tongue were elicited. Bilateral contractions of the masticatory muscles, while not pronounced, were quite evident, and were always accompanied by movements of the superficial facial muscles. With the exception of the masticatory muscles, the movements were exclusively contralateral. Stimulation of an area (fig. 2 *H*) at the lower end of the cruciate sulcus elicited a complex movement of the superficial muscles of the face and neck. It is best designated as a unilateral snarling movement (fig. 8). There were retraction and elevation of the upper lip which caused a wrinkling of the skin over the side of the nose and exposure of the upper teeth. At the same time there occurred retraction of the corner of the mouth, a pulling down of the lower lip exposing the lower teeth and a simultaneous drawing of the rhinarium toward the contralateral side. The ear was pulled backward and toward the midline by contraction of the posterior auriculo-occipital musculature, and the eye was closed by contraction of the orbicularis oculi. Except for the closure of the eye, this movement was certainly of the type which one sees in carnivores that snarl. It consisted of a complicated coordinated muscular movement of almost the entire superficial muscles of the face and neck.

At the antero-inferior end of the motor cortex (fig. 2 *L*) stimulation elicited the snarling movement accompanied by movements of the tongue

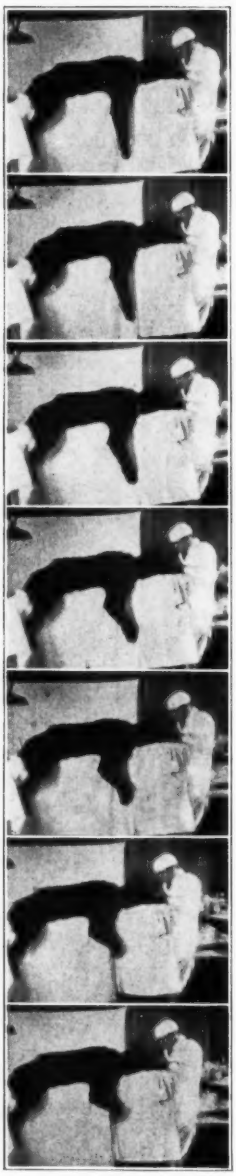

Fig. 6

Fig. 7

Fig. 8

Fig. 6.—The complex movement of the contralateral foreleg elicited from area *F* (fig. 2).

Fig. 7.—The movement elicited from area *G* (fig. 2). Turning of the head to the contralateral side; slight contraction of the facial musculature.

Fig. 8.—The contralateral snarling movement elicited from area *H* (fig. 2).

and larynx. In addition to the movements in the facial muscles, the tongue was curved toward the contralateral side, and the posterior part of it became markedly elevated and thus laid against the palate. At the same time the larynx moved anteriorly and respirations temporarily ceased. On removal of the electrode, the larynx, tongue and facial muscles returned to their former position. The cessation of respirations was apparently due to the upward movement of the larynx and the subsequent closure of its upper aperture, as occurs in the act of swallowing. The elevation of the posterior part of the tongue and the upward movement of the larynx together with the temporary cessation of respiration seemed to indicate that this movement was fundamentally the act of swallowing.

On stimulation just anterior to the lateral end of the cruciate sulcus (fig. 2 *J*) another type of facial movement was observed. This movement is difficult to describe and was not reproduced in the motion picture. It was a rather isolated movement composed of a strong drawing in at the base of the nasal septum, thus making a depression at that point and a simultaneous protrusion of the upper lip. It was as though the bear was reaching out after an object with his upper lip or was protruding the upper lip and endeavoring to sniff the air. This movement often went over into a more general response such as was elicited by stimulation at area *K*, which gave retraction and elevation of the upper lip. The movements elicited from area *K* therefore contained only the upper lip components of the snarling movement.

Exploration of the entire remainder of the exposed cerebral cortex gave no response.

HISTOLOGY OF THE MOTOR CORTEX

Before proceeding to a histologic description of the motor areas in the cerebral cortex of the bear, it may be well to review briefly the fundamental studies on which the present concept of cerebral cortical architecture has been built.

Ideas concerning cortical lamination may be said to have begun with the discoveries of Gennari. According to Campbell,[12] Gennari discovered and gave an accurate description of the "lineola albidior admodum eleganter," in the calcarine region of the brain. About ten years later, Vicq d'Azyr,[13] apparently unaware of Gennari's discovery, rediscovered the same lines, and in his large treatise on anatomy described and figured in colored plates the bands of white substance in the gray matter of the visual cortex. Baillarger[14] believed that the

12. Campbell, A. W.: Histological Studies on the Localisation of Cerebral Function, London, Cambridge University Press, 1905.

13. Vicq d'Azyr, Félix: Traité d'anatomie et de physiologie, Paris, F.-A. Didot l'ainé, 1786.

14. Baillarger, J.: Recherches sur la structure de la couche corticale des circonvolutions du cerveau, Mém. de Acad. roy. de méd. **8**:149, 1840.

cerebral cortex presented six distinct laminae, arranged in layers of alternating white and gray matter from without inward. These classifications of laminae, based on macroscopic observation, necessarily had to give way to a new classification based on more critical analyses by microscopic methods. With the improved microscopic methods of study, new cortical subdivisions were made, and while the earlier workers had based their scheme of lamination chiefly on fiber layers, the later workers considered cell stratification of more importance. Thus it was that Meynert,[15] supported by Betz,[16] rejected the findings of previous investigators and claimed that the cortex which possessed five cell layers was the most extensive. Lewis and Clarke,[17] after careful investigations, came to the conclusion that in man the precentral gyrus exhibited five layers, but that most other portions of the cortex possessed a six-layered arrangement. Campbell,[12] from extensive studies on the human brain, came to the conclusion that a seven-layered type was the most widespread. Brodmann,[18] after studying the cortical structure of a large number of mammals, including man, decided that a six-layered cortex was the fundamental type. Economo,[19] in his study of the cyto-architectonics of the human cerebral cortex, adopted Brodmann's classification.

Early in the study of the cerebral cortex it became apparent that all areas of the cortex were not of the same thickness and did not show the same arrangement of cell laminae. In addition, certain areas were characterized by cells not to be found in any other region. On the basis of these differences investigators began to study different areas in order to determine the structure characteristic of the different regions. Thus it was that Betz,[16] stimulated by the epochal demonstration by Fritsch and Hitzig [11] in 1870 that electrical excitation of certain areas in the cerebral cortex of the dog produced muscular movements in various parts of the body, turned to a microscopic study of the cortex with the avowed intention of determining the relation between the different parts of the brain in man and in animals. From his histologic studies on the brain of man, Betz [16] made the important observation that the anterior central gyrus contained multipolar cells which had not been described by any previous investigator and which because of

15. Meynert, T.: The Brain of Mammals, in Stricker, S.: Manual of Histology, New York, William Wood & Company, 1872.

16. Betz, W.: Anatomischer Nachweis zweier Gehirncentra, Centralbl. f. d. med. Wissensch. **12**:578 and 595, 1874.

17. Lewis, B., and Clarke, H.: The Cortical Lamination of the Motor Area of the Brain, Proc. Roy. Soc., London **27**:38, 1878.

18. Brodmann, Korbinian: Vergleichende Lokalisationslehre der Grosshirnrinde, Leipzig, Johann Ambrosius Barth, 1909.

19. von Economo, Constantin: Zellaufbau der Grosshirnrinde des Menschen, Berlin, Julius Springer, 1927.

their large size he named giant pyramidal cells. These cells were located in the layer of the cortex corresponding to the fifth layer, if one accepts the six-layered classification of Brodmann. Betz, from his careful study of this region in man and the apes, concluded that these giant pyramidal cells had the significance of motor cells.

Later investigators, among whom may be mentioned Campbell,[12] Brodmann [18] and Economo,[19] carefully studied the cerebral cortex and plotted on its surface the extent of the areas differing in histologic structure. On the basis of cellular arrangement, Campbell [12] divided the human cerebral cortex into fourteen different regions or areas, Brodmann into about fifty, and Economo into more than one hundred. Hence it can be seen that great disagreement exists as to the number of areas separately recognized. In spite of this disagreement, there is sufficient evidence to show that each of the different cortical regions in each mammalian order has a definite structural pattern which is characteristic.

In the division of the cerebral cortex into layers, it must be borne in mind that the number of layers into which one can divide the cortex depends largely on the criteria and ability of the investigator. According to Economo,[19] the six layers of Brodmann in some parts of the human cortex may be easily increased to ten. In addition, one type of cortex does not abruptly end where another begins, but a more or less gradual transition occurs between one type and another. Furthermore, the cortical layers are most easily recognized in the human cerebral cortex. The lower one goes in the mammalian scale, the more difficult becomes the subdivision into six layers.

If one examines a section from an area of a cerebral cortex which belongs to the six-layered type (fig. 9*A*), one sees a granular layer consisting of closely packed, small, round, stellate or triangular, granule-like cells interposed between two layers of conspicuous pyramidal cells. This granular layer of Bolton corresponds to the lamina granularis interna, layer IV of Brodmann. All the cells lying above this layer are designated as supragranular, while all those lying below are designated as infragranular. The supragranular lamina may be subdivided into two layers: an inner one, the lamina pyramidalis, layer III of Brodmann, consisting of medium-sized and large pyramidal cells, and an outer layer, the lamina granularis externa, layer II of Brodmann, consisting of numerous densely packed granule-like cells similar to those found in layer IV. The outermost layer of the cerebral cortex, the lamina zonalis or plexiformis, layer I of Brodmann, consists chiefly of nerve fibers with only a few nerve cells. In the infragranular layer two subdivisions may be recognized. Just below the granular layer there is situated a layer of large and medium-sized pyramidal cells, the lamina ganglionaris, layer V of Brodmann. Except in the cortex of

the motor area, the pyramidal cells in layer V hardly ever reach the size of the pyramidal cells in layer III. In the fifth layer of the motor cortex of mammals is situated the largest of all cortical cells, the giant pyramidal cell of Betz. At the present time evidence indicates that the axons of the pyramidal cells in this layer enter the corticospinal and corticobulbar tracts. The second layer of the infragranular lamina is the lamina multiformis, layer VI of Brodmann, consisting of fusiform cells, many of which are placed perpendicularly to the cortical surface.

Bolton,[20] from embryologic studies, found that the infragranular layer is the first to develop. Soon after this the granular layer develops, and still later differentiation of the supragranular layer occurs. From careful cyto-architectonic studies of the brains of psychiatric patients, Bolton concluded that in amentia the supragranular layer was poorly developed, and in dementia it was the first to undergo degeneration.

The comparative histologic and phylogenetic studies of Mott,[21] Watson,[22] Ariëns Kappers,[23] van't Hoog [24] and others show that the supragranular layer is poorly developed in lower mammalian forms, and that the cells become numerous only in the cortices of higher mammals, reaching their greatest development in man. It therefore appears, from embryologic, pathologic and phylogenetic studies, that the supragranular layer must be considered as the one concerned with the highest cerebral processes.

In experiments on electrical stimulation of the cerebral cortex carried out under proper experimental conditions so as to avoid spreading of the current, only that portion of the cortex which lies exposed on the surface of the brain can be stimulated. That portion of the motor cortex which forms the walls of the cruciate sulcus and which in the bear is much greater in extent than the exposed motor cortex is not stimulated in ordinary experiments on stimulation. Therefore, only those sections of the motor cortex taken from the crown of the gyri show regions which have been stimulated under the conditions prevail-

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20. Bolton, J. S.: The Histological Basis of Amentia and Dementia, Arch. Neurol. **2**:424, 1903; The Brain in Health and Disease, London, Edward Arnold & Co., 1914.

21. Mott, F. W.: The Progressive Evolution of the Structure and Functions of the Visual Cortex in Mammalia, Arch. Neurol. **3**:1, 1907.

22. Watson, G. A.: The Mammalian Cerebral Cortex, with Special Reference to Its Comparative Histology: 1. Order Insectivora, Arch. Neurol. **3**:49, 1907.

23. Ariëns Kappers, C. U.: The Phylogenesis of the Palaeo-Cortex and Archi-Cortex Compared with the Evolution of the Visual Neo-Cortex, Arch. Neurol. & Psychiat. (London) **4**:161, 1909; Die vergleichende Anatomie des Nervensystems der Wirbeltiere und des Menschen, Haarlem, de Erven F. Bohn, 1921; The Development of the Cortex and the Functions of Its Different Layers, Acta psychiat. et neurol. **3**:115, 1928.

24. van't Hoog, E. G.: On Deep Localization in the Cerebral Cortex, J. Nerv. & Ment. Dis. **51**:313, 1920.

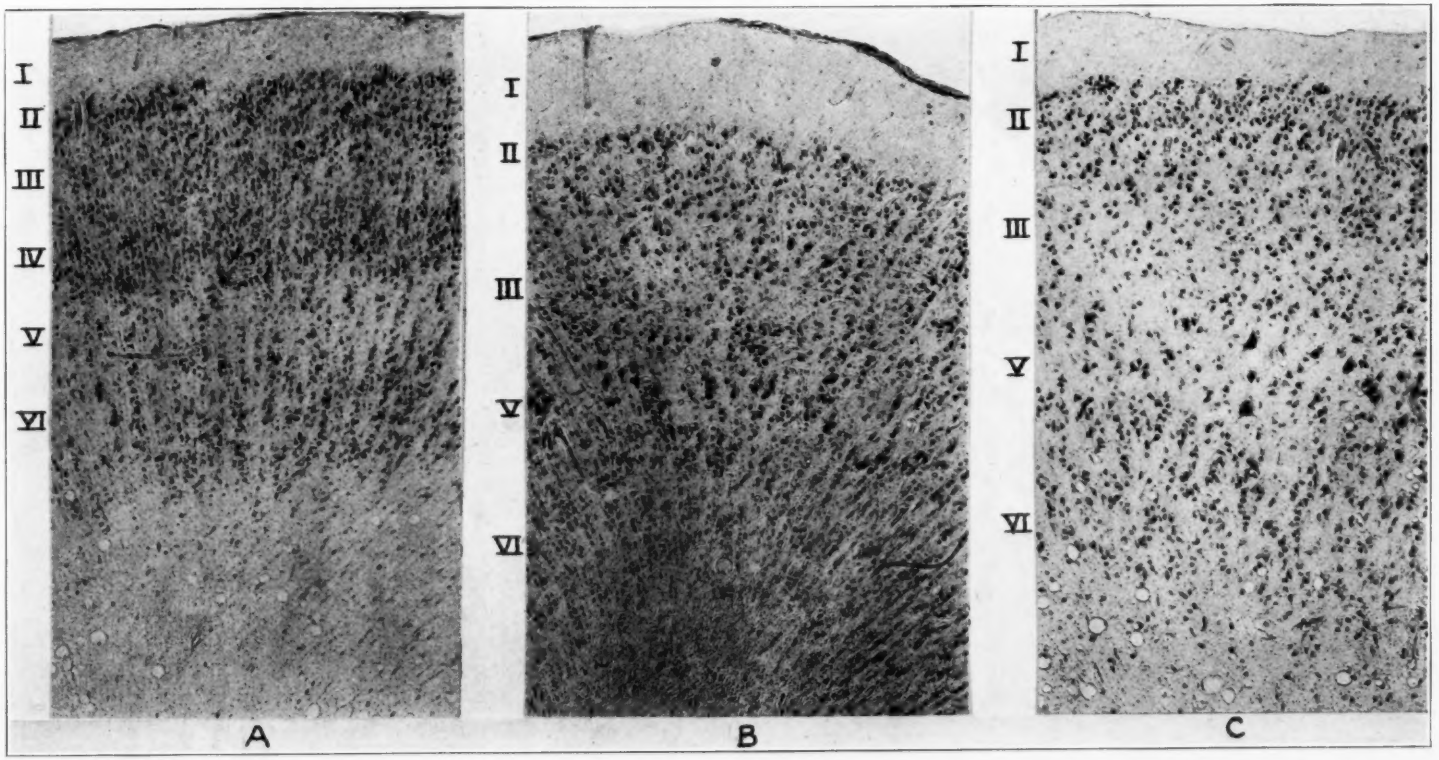

Fig. 9.—Sections 25 microns thick; thionine stain; × 30. *A*, the cortex of the coronal sulcus, showing the six-layered type of cortex. *B*, the cortex of the hindleg area. *C*, the cortex of the foreleg area.

ing during this experimental study. Sections from that portion of the motor cortex forming the walls of the cruciate sulcus will be figured also in order to show the changes which the cortical structure undergoes as it approaches the depth of the sulcus. All the sections were taken as nearly perpendicular to the sulcus and to the cortical surface as was possible. Only when this condition is fulfilled is one able to compare with any degree of accuracy the thickness of the cortex in different areas. The distinctness of the cell lamination in the cerebral cortex depends to some extent on the thickness at which the sections are cut. Economo [19] found that in the human brain the optimum thickness was 25 microns. Sections of the cerebral cortex of the bear were cut from 5 to 40 microns in thickness and stained with thionine. From an examination of these sections it became evident that sections 25 microns thick showed the cell lamination most clearly. Therefore, all the photomicrographs are made from sections 25 microns in thickness and stained with thionine.

As has been shown by various investigators for other mammals, the motor cortex of the bear has a cyto-architectural structure that is strikingly different from that of the remainder of the cerebral cortex. In the motor cortex of the bear one sees the result of a process termed by Economo [19] in the case of man "pyramidization"; i. e., most of the granule cells have been replaced by cells which are definitely pyramidal in shape. This has resulted in an almost complete disappearance of the granule layers, with a resulting accentuation of the layers which in other parts of the cortex contain chiefly pyramidal cells.

CHARACTERISTICS OF THE MOTOR CORTEX

The characteristic structure of the motor cortex on the surface of the cerebral hemisphere is seen in sections taken from the cortical areas of the hindleg, foreleg and facial-masticatory muscles (fig. 9 *B* and *C*; fig. 10 *A*). Layer I, the plexiform layer, contains few nerve cells, and although it is rather wide it possesses no feature distinctive of the motor area. Layer II, the internal granular layer, is quite narrow and is richer in nerve cells than any other layer, and hence appears as the most compact layer present. In it may still be seen some of the small rounded or stellate granule cells, but the many granule cells which characterize this area in most of the nonmotor cortex have been replaced by small pyramidal cells. The third or external pyramidal layer is the widest layer in the motor cortex. It is distinctly poorer in cells than the second layer, but the cells are larger and almost all are pyramidal in shape. In this layer the larger pyramidal cells tend to occur near its inner margin, and in the inner zone of this layer the cells are much sparser than in the outer zone. Layer IV, the internal granular layer, has also undergone pyramidization and is not present; the few granule cells representing this layer are sparsely scattered among the pyramidal cells at the junction of layer III and layer V. The external layer of the infragranular part of the cerebral cortex is layer V, or the lamina ganglionaris of Brodmann. In this layer, comparatively poor in cells, there occurs the most conspicuous feature of the motor cortex, the giant pyramidal cells of Betz. The pyramidal cells of layer V

in cortical regions other than the motor cortex seldom attain the size of those found in layer III. The giant cells are pyramidal or pyriform, and each possesses an apical dendrite which passes up toward the cortical surface and several other processes which come off the cell body at various points. Each contains a nucleus which is relatively small in proportion to the size of the cell, and the cell body is normally filled with large chromophilic granules. This ganglionic layer of cells occurs throughout the entire motor cortex, but giant cells are not present in all motor areas. The largest cells are usually found in the areas of the extremities. The large pyramidal cells of layer V often tend to be grouped together in nests. Along the top of the posterior sigmoid gyrus, nests containing two or more giant cells occur at irregular intervals in layer V, but as the bottom of the cruciate sulcus is approached the giant cells lose this nestlike arrangement and appear in solitary formation (fig. 10 *B*). In addition, the cortex in the motor area, as in other regions, becomes gradually narrowed as it dips deeper and deeper into the sulcus, so that at the bottom of the sulcus the depth of the cortex is only a fraction of that at the surface of the brain, and all the layers are much poorer in cells (fig. 10 *B*). As the cortex passes around the bottom of the cruciate sulcus, the cells of the sixth layer assume a position that is parallel to the cortical surface. After passing around the bend of the sulcus, the giant cells continue for a short distance up the anterior wall and become smaller and less numerous as they approach the surface. At a short distance from the top of the sulcus they entirely disappear as the motor cortex gradually changes over into the nonmotor type of cortex characteristic of the arctoid lozenge. In the upper part of the hindleg area the motor cortex on the anterior wall of the cruciate sulcus ceases about 1 cm. from the top of the sulcus, but as one passes more laterad on the arctoid lozenge the motor cortex anteriorly gradually approaches the surface, until just beyond the lateral end of the arctoid lozenge it appears on the surface of the hemisphere in the anterior sigmoid gyrus. The innermost layer of the infragranular lamina, layer VI, the fusiform layer, consists of a mixture of polygonal, round and fusiform cells. In the motor area this layer tends to be narrower than in most other regions of the cortex, and the cells become less numerous as the white matter is approached. The fusiform cell of this layer has an oval nucleus containing a distinct nucleolus. The Nissl granules are collected about both poles of the nucleus.

The Arctoid Lozenge: That part of the cortex called by Mivart the ursine lozenge, but which I prefer to designate as the arctoid lozenge, and which proved inexcitable to electrical stimulation, has a cyto-architectural structure definitely not motor in type but corresponding rather to the nonmotor agranular frontal type of Brodmann (fig. 10 *C*). A section through the lozenge taken perpendicular to its surface and perpendicular to the cruciate sulcus shows a cell lamination distinctly different from that of the cortex of the motor area. The thickness of the cortex approximates that in the motor area, but the pyramidal cells in layers III and V are distinctly smaller. The internal granular layer is absent, and the pyramidal cells of layers III and V are not so large as those in the corresponding layers of the motor cortex. Cell lamination is not nearly so clear as in the motor cortex. The cells are more evenly distributed and are more numerous than in the motor areas. Only rarely are clusters of cells found in the fifth layer of the cortex of the arctoid lozenge. Such a group may be seen in the center of the photomicrograph through this part of the cortex. At first glance it appears as though large cells are present, but on closer examination several small pyramidal cells can be seen making up the cluster.

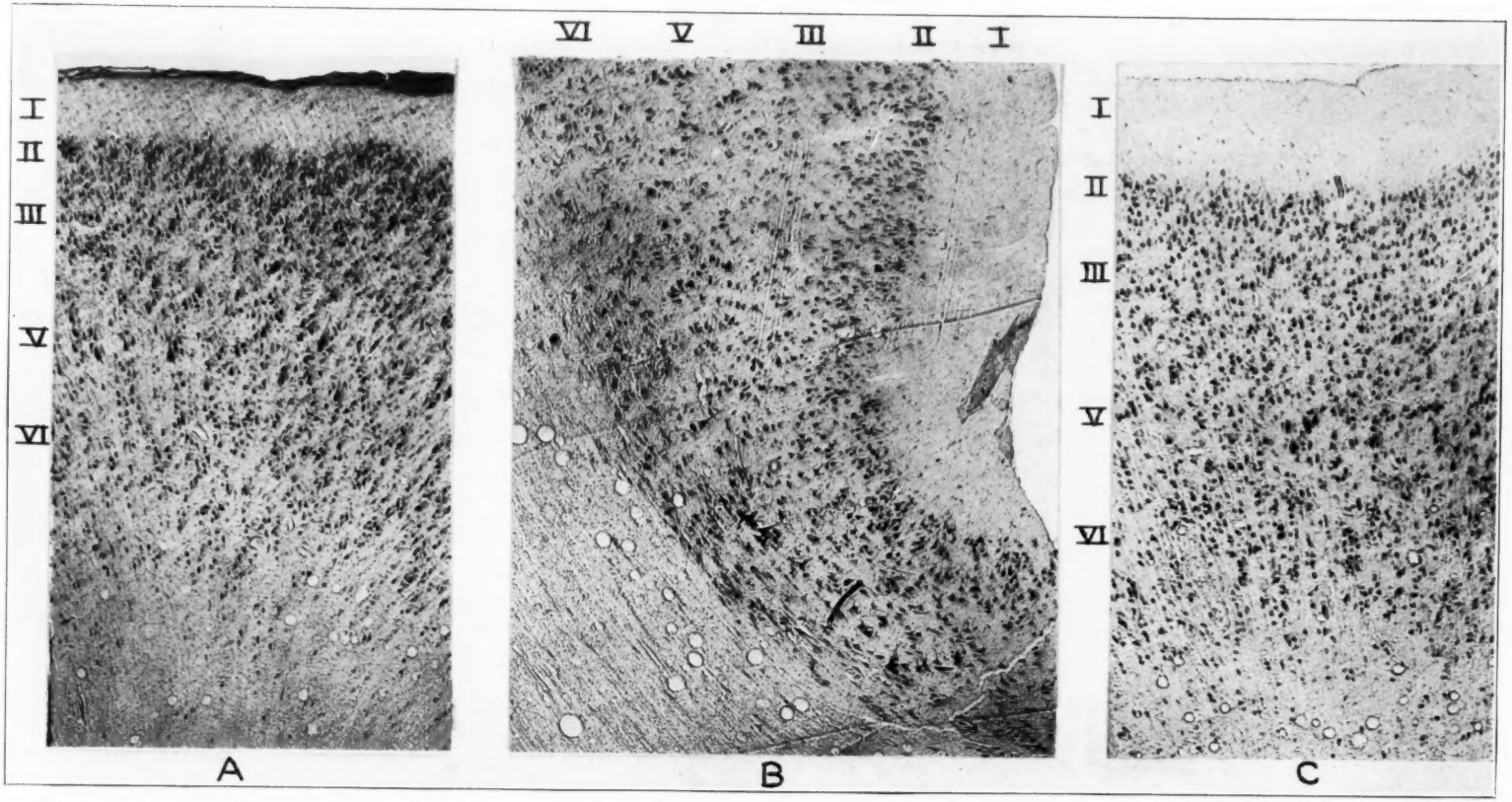

Fig. 10.—Sections 25 microns thick; thionine stain; × 30. *A*, the cortex of the facial-masticatory area. *B*, the cortex of the posterior wall of the cruciate sulcus in the foreleg area, showing the changes that take place as the bottom of the sulcus is approached. *C*, the cortex of the arctoid lozenge, the agranular frontal type of Brodmann.

Extent of the Motor Cortex.—In order to determine the extent of the motor area histologically, blocks of tissue were taken through the entire length of the cruciate sulcus. In removing these blocks the utmost care was taken to get them so that the sections would be perpendicular to the surface of the cortex and to the walls of the cruciate sulcus. The sections were cut 25 microns thick and stained with thionine.

The extent of the motor cortex on the lateral cerebral surface as revealed by histologic examination and its extent as determined by the physiologic method are apparently identical. Sulci cannot be considered to demarcate the motor area accurately. In the upper part of the motor cortex the postcruciate sulcus approaches the cruciate. At this point the motor cortex dips down into the postcruciate sulcus, and hence this part of the cortex in the hindleg region was inaccessible to stimulation. More laterally the postcruciate sulcus is separated from the cruciate sulcus by a greater expanse of cerebral cortex, and in this region the motor cortex does not extend to the postcruciate sulcus. The motor cortex dips into the lateral end of the postcruciate sulcus and on its anterior wall changes from a motor to a nonmotor type. In a similar manner it dips down into the coronal sulcus and passes around the bottom of the sulcus, gradually changing into the six-layered type seen in the coronal gyrus (fig. 9*A*). The motor region extends around the lateral end of the cruciate sulcus and, as a gradually narrowing strip of cortex, reaches the lateral border of the arctoid lozenge. At this point the motor cortex disappears from the surface of the brain, gradually receding lower and lower on the anterior wall of the cruciate sulcus. In the region of the hindleg area, on the anterior wall of the cruciate sulcus near the bottom, the motor cortex passes over into the nonmotor agranular frontal type of the arctoid lozenge.

The extent of the motor cortex on the exposed surface of the brain as outlined by the physiologic method of faradic stimulation corresponds to its extent as revealed by histologic examination. In brains containing deep sulci the extent of the motor cortex cannot be ascertained physiologically, because it dips down into sulci which intrude into its domain, and this part of the motor cortex is not stimulated under ordinary experimental conditions. It is evident that sulci do not form the limits of the motor cortex. Because sulci and gyri are the result of so many evolutionary and physical factors, they necessarily vary not only from species to species, but also from animal to animal in the same species, and they cannot be considered to form sharp boundaries for the motor cortex. Variations in the gyri and sulci among individuals of the same species may help to explain slight differences in extent and position of the motor areas as obtained by different investigators.

COMMENT

Stimulation of the cerebral cortex in the bear, as well as in all other mammals, produces contraction in groups of muscles resulting in definite muscular movements. Because the movements executed usually resemble in a greater or a lesser degree those which the animal performs in his daily activity, they have been designated as purposeful

movements; i. e., they appear as though intentionally executed for a definite purpose. As a general rule, they resemble closely set types which probably have their pattern arranged in the cortical areas that control the movements ordinarily performed by the animal in his daily activity.

As one ascends the mammalian scale, passing from mammals of the lowest order (monotremes) to those of the highest order (man), it becomes clear that the motor cortex becomes more highly developed, both as regards its histologic structure and also as regards the localization of definite movements within the motor area.

Martin [25] stimulated the cerebral cortex of one of the monotremes, the duckbill platypus (Ornithorhynchus), and found an ill-defined motor area which yielded movements of the facial and foreleg muscles. The areas yielding facial and foreleg movements partly coincided, while no area for the hindleg and tail could be demonstrated.

Among the marsupials, the opossum (Didelphys virginiana) has been most frequently studied. All investigators agree that movements of the facial and foreleg musculature are regularly obtained. Herrick and Tight,[26] Ziehen [27] and C. and O. Vogt [28] obtained movements of the hindlegs, but only with much difficulty and by using a current much stronger than that necessary to elicit responses in the face and foreleg. The findings of these investigators as regards the hindleg are in direct opposition to those of Cunningham,[29] Rogers,[30] Gray and Turner,[31] Weed and Langworthy [32] and Langworthy,[33] who never obtained movements of the hindlegs or the tail. In several opossums which I have subjected to stimulation no movements of the hindleg were obtained.

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25. Martin, C. J.: Cortical Localization in Ornithorhynchus, J. Physiol. **23**: 383, 1898.

26. Herrick, C. L., and Tight, W. G.: The Central Nervous System of Rodents, Bull. Sc. Lab. Denison Univ. **5**:35, 1890.

27. Ziehen, T.: Ueber die motorische Rindenregion von Didelphys virginiana, Centralbl. f. Physiol. **11**:457, 1897.

28. Vogt, C., and Vogt, O.: Zur Kenntnis der elektrisch erregbaren Hirnrinden-Gebiete bei den Säugetieren, J. f. Psychol. u. Neurol. **8**:277, 1907.

29. Cunningham, R. H.: The Cortical Motor Centres of the Opossum (Didelphys Virginiana), Am. J. Physiol. **22**:264, 1897-1898.

30. Rogers, F. T.: An Experimental Study of the Cerebral Physiology of the Virginian Opossum, J. Comp. Neurol. **37**:265, 1924.

31. Gray, P. A., and Turner, E. L.: The Motor Cortex of the Opossum, J. Comp. Neurol. **36**:375, 1924.

32. Weed, L. H., and Langworthy, O. R.: Developmental Study of Excitatory Areas in the Cerebral Cortex of the Opossum, Am. J. Physiol. **72**:8, 1925.

33. Langworthy, O. R.: Correlated Physiological and Morphological Studies of the Development of Electrically Responsive Areas in the Cerebral Cortex of the Opossum, Contrib. Embryol. (no. 103) **19**:149, 1927.

Only one species of the entire order of insectivores has been subjected to cortical stimulation, the European hedgehog (Erinaceus europaeus). Analysis of the results obtained from stimulation of the cerebral cortex of this animal by Mann,[34] Ziehen,[27] Probst [35] and C. and O. Vogt [28] leaves one uncertain as to exactly what musculature is represented in the cerebral motor cortex of this mammal. It seems that simple movements of the facial and foreleg musculature are easily obtained, while movements of the hindleg are obtained with much more difficulty, if at all.

The motor cortex of the rodents has been investigated much more than that of any of the mammals previously mentioned. The animals which have been most frequently investigated include the rat, rabbit and guinea-pig. A study of the results obtained by Ferrier,[36] Fürstner,[37] Bechterew,[38] Exner and Paneth,[39] Mann,[34] Ziehen,[27] Simpson [40] and Lashley [41] discloses the fact that contradictory results have been obtained. From these investigations it must be concluded that the motor cortex of these mammals is not well defined, and that the movements elicited may vary from one animal to another of the same species. Movements of the facial, masticatory and foreleg musculature are regularly obtained, but investigators disagree as to whether or not the hindleg is represented in the motor cortex.

As representatives of the ungulates, the sheep and goat have been studied by various investigators, including Ziehen,[42] Dexler and Margulies,[43] Simpson and King [44] and Bagley.[45] There is little agreement

34. Mann, G.: On the Homoplasty of the Brain of Rodents, Insectivores, and Carnivores, J. Anat. & Physiol. **30**:1, 1896.

35. Probst, M.: Ueber den Hirnmechanismus der Motilität, Jahrb. f. Psychiat. **20**:181, 1901.

36. Ferrier, D.: The Function of the Brain, New York, G. P. Putnam's Sons, 1880 and 1886.

37. Fürstner, C.: Experimenteller Beitrag zur elektrischen Reizung der Hirnrinde, Arch. f. Psychiat. **6**:719, 1876.

38. von Bechterew, W.: Die Funktionen der Nervencentra, Jena, 1911.

39. Exner, S., and Paneth, J.: Das Rindenfeld des Facialis und seine Verbindungen bei Hund und Kaninchen, Arch. f. d. ges. Physiol. **41**:349, 1887.

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41. Lashley, K. S.: Studies of Cerebral Function in Learning: III. The Motor Areas, Brain **44**:255, 1921.

42. Ziehen, T.: Ein Beitrag zur Lehre von den Zeziehungen zwischen Lage und Function im Bereich der motorischen Region der Grosshirnrinde mit specieller Rücksicht auf das Rindenfeld des Orbicularis oculi, Arch. f. Physiol., 1899, p. 158.

43. Dexler, H., and Margulies, A.: Ueber die Pyramidenbahn des Schafes und der Ziege, Morphol. Jahrb. **35**:413, 1906.

44. Simpson, S., and King, J. L.: Localisation of the Motor Area in the Sheep, Quart. J. Exper. Physiol. **4**:53, 1911.

45. Bagley, Charles, Jr.: Cortical Motor Mechanism of the Sheep Brain, Arch. Neurol. & Psychiat. **7**:417 (April) 1922.

among the results obtained by the different investigators. While disagreeing as to the exact position and extent of the various areas, most investigators found an area representing the facial muscles, another for the foreleg and another for the hindleg. Response from the hindleg, however, was more difficult to obtain than from the face or the foreleg.

Investigations of the motor cortex of carnivores, especially the cat, and the dog, carried out by many investigators, including Fritsch and Hitzig,[11] Ferrier,[36] Hitzig,[46] Paneth,[47] Bechterew,[38] Exner and Paneth,[39] Herrick and Tight,[26] Mann,[34] Weed and Langworthy [48] and Langworthy [49] and my own unpublished investigations clearly demonstrate that in the carnivores the motor cortex has become more definitely localized than in the lower mammalian orders, and that the hindleg is regularly represented in addition to the face, neck and foreleg. In the motor cortex of the carnivores the different groups of muscles which respond to electrical stimulation are represented by more definite and much better localized areas in the cortex than is the case in the lower mammalian orders.

In the cat the motor area occupies a definite position, being found in the cortex of the anterior and posterior sigmoid gyri which surround the cruciate sulcus. The foreleg area is situated in the anterior sigmoid gyrus, the hindleg area behind the cruciate sulcus in the upper part of the posterior sigmoid gyrus, and the facial-masticatory area in the lower part of the anterior sigmoid gyrus. Investigations on the motor cortex of the cat show that the motor cortex in the anterior sigmoid gyrus reaches the medial edge of the hemisphere. The gyrus proreus, situated in front of the anterior sigmoid gyrus and lying against the medial edge of the hemisphere, has a cyto-architectural structure which shows that it belongs not to the motor cortex, but to that part of the cortex designated by Campbell [12] and Langworthy [50] as the area frontalis, and by Brodmann [18] as the area frontalis agranularis.

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46. Hitzig, Eduard: Physiologische und klinische Untersuchungen über das Gehirn, Berlin, A. Hirschwald, 1904.

47. Paneth, J.: Ueber Lage, Ausdehnung und Bedeutung der absoluten motorischen Felder auf der Hirnoberfläche des Hundes, Arch. f. d. ges. Physiol. **37:** 523, 1885.

48. Weed, L. H., and Langworthy, O. R.: Physiological Study of Cortical Motor Areas in Young Kittens and in Adult Cats, Contrib. Embryol. (no. 362) **17:**89, 1926.

49. Langworthy, O. R.: Histological Development of Cerebral Motor Areas in Young Kittens Correlated with Their Physiological Reaction to Electrical Stimulation, Contrib. Embryol. (no. 104) **19:**177, 1927.

50. Langworthy, O. R.: The Area Frontalis of the Cerebral Cortex of the Cat, Its Minute Structure and Physiological Evidence of Its Control of the Postural Reflex, Bull. Johns Hopkins Hosp. **42:**20, 1928.

My own investigations on the dog reveal that an area of cortex in that part of the anterior sigmoid gyrus adjacent to the longitudinal cerebral fissure is unresponsive to electrical stimulation. The histologic structure of this unresponsive area shows that it belongs to the area frontalis. Not only has the area frontalis increased in size in the dog so that it occupies a considerable area in the anterior sigmoid gyrus, but a change in the position of the motor areas has also occurred, the foreleg area being situated in the posterior sigmoid gyrus. In the dog, therefore, the motor cortex is situated in the cortex of the posterior sigmoid gyrus and in the cortex surrounding the lateral end of the cruciate sulcus.

Electrical stimulation of the cerebral cortex in the bear showed that the motor cortex is limited to the posterior sigmoid gyrus and to the cortex surrounding the lower end of the cruciate sulcus. It is to be noted that the distribution of the motor areas in the bear corresponds more closely to their position in the dog than in the cat. Furthermore, the movements obtained from the cortex of the bear resembled those elicited from the cerebral cortex of the dog more closely than those obtained from the cat.

The foreleg area in the bear is much greater in extent than the hindleg area. In addition, a greater number of movements may be elicited from the foreleg area than from the hindleg region. This shows that a greater differentiation of movements has occurred in the foreleg area. The facts that the foreleg area is so much larger than the hindleg area and that the movements elicited from it are more complex can undoubtedly be correlated with the much greater use which the bear makes of the foreleg. Any one who has observed bears in their daily activity is well acquainted with the fact that they use the foreleg and paw in a very dextrous manner. They are able to pick up quite small particles of food in the paw and convey it to their mouths.

The differentiation of movement in the facial-masticatory area has apparently not evolved very high. The snarling movement results from a contralateral contraction of practically the entire group of superficial muscles innervated by the facial nerve. Not only does contraction occur in all the superficial muscles of the face, but the cervical portion of the platysma and its derivative the posterior auriculo-occipital musculature also contract. Contraction of the posterior auriculo-occipital musculature pulls the ear back and toward the midline.

SUMMARY AND CONCLUSIONS

A physiologic and histologic study of the cerebral cortex of the bear demonstrates that the motor area is confined to the cortex of the posterior sigmoid gyrus and the cortex surrounding the lateral end of the cruciate sulcus. Areas for the musculature of the hindleg and tail, the foreleg, the neck, the facial-masticatory region, the tongue and

the larynx were mapped out. The relative positions of the areas are similar to the positions in the primates, including man; i. e., the area for the musculature of the hindleg is situated near the medial edge of the hemisphere, and as one passes laterad one finds the areas for the musculatures of the foreleg, the neck, the facial-masticatory region and the tongue and larynx in the order named.

The majority of responses elicited from the left side of the cortex were recorded cinematographically and appeared to be identical with those elicited from the right side.

Contralateral and ipsilateral movements of the hindlegs and movements of the tail were obtained from the superior part of the posterior sigmoid gyrus. Contralateral movements of the foreleg were elicited from an area lying inferior and lateral to the hindleg area. The foreleg area was much larger than the hindleg area, and the movements elicited were more diversified. The larger size of the foreleg area and the greater diversity of movements obtained from it can probably be correlated with the greater use which the bear makes of the forelegs.

Contralateral contractions of the cervical, facial, lingual and laryngeal muscles were obtained from certain areas of the cortex around the inferior lateral end of the cruciate sulcus; moreover, bilateral contraction of the masticatory muscles was obtained on stimulation of the facial area. The movements obtained from these areas did not appear so well differentiated, nor were the areas of the cortex so well defined, as in the case of the foreleg area.

The extent of the motor cortex on the exposed surface of the brain as determined by histologic examination corresponds to its extent as revealed by the physiologic method of faradic stimulation.

In the brains of mammals such as the bear, in which the cruciate sulcus is very deep, the entire extent of the motor cortex cannot be obtained by the physiologic method. The motor cortex dips down into the sulci (cruciate, postcruciate and coronal) which intrude in its domain, and this part of the motor cortex is not accessible to stimulation under ordinary experimental conditions.

The variations in the gyri and sulci among individuals of the same species may help to explain the slight differences in the extent and position of the motor cortex as obtained by the physiologic method. Therefore, determination of the extent of the motor cortex should always be checked by a histologic study.

That area of the cortex known as the arctoid lozenge which lies anterior to the cruciate sulcus is unresponsive to electrical stimulation. Histologic study shows that it has a cyto-architectural structure that is nonmotor in type. It belongs to the area frontalis agranularis of Brodmann.

In the cat the motor cortex in the anterior sigmoid gyrus reaches the medial edge of the hemisphere. In the dog the upper or more medial part of the anterior sigmoid gyrus does not contain motor cortex, but consists of unresponsive cortex of the agranular frontal type. In the bear the agranular frontal cortex occupies a considerable portion of the region of the anterior sigmoid gyrus and is much greater in extent than in the cat and the dog.

Anatomic, physiologic and histologic study of the electrically responsive cortex of the bear leads to the conclusion that it shows a higher state of development than is present in the other carnivores which have been most frequently studied, the cat and the dog.

Dr. George W. Corner rendered valuable assistance in this work, and Dr. Robert K. Burns, Jr., Dr. Roland K. Meyer and Mr. Adrian Buyse aided in the experiments.

STUDIES ON THE CEREBRAL CORTEX

I. LOCALIZED CONTROL OF PLACING AND HOPPING REACTIONS IN THE CAT AND THEIR NORMAL MANAGEMENT BY SMALL CORTICAL REMNANTS

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THE POSTURAL ABNORMALITIES OF DECORTICATE CATS

One of the most striking abnormalities exhibited by four cats without cerebral cortex throughout periods of survival ranging from six weeks to twenty-eight months was a tendency to assume peculiar attitudes of the legs while standing, sitting or crouching. The most prominent defects of attitude were crossing, abduction or retroposition of the forelegs and abduction or forward displacement of the hindlegs. These static abnormalities contrasted conspicuously with the relative normality of locomotion seen in the decorticate cat. They commonly developed after the animal had remained for some time in a standing, crouching or sitting position, and then the peculiar attitude of the leg was often the result of an uncorrected sliding of the foot away from its normal position. Another event favoring their appearance was the premature cessation of some movement: for example, a normally executed act of scratching might cease without withdrawal of the hindfoot to its normal position, and as a result the cat might remain for many minutes with that foot held too far forward at the end of a rigidly extended leg. Similarly, walking might cease abruptly just as a leg had completed the forward or backward phase of the step, whereon the foot was very likely to remain too far advanced or too far retroplaced, and this abnormal position sometimes continued after the animal

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Read at a meeting of the Association for Research in Nervous and Mental Disease, New York, Dec. 28, 1932.

From the Physiological Laboratory, Princeton University and the Laboratories of Physiology, Harvard Medical School.

This paper is a full account of work which has been in part communicated in the following preliminary reports: (*a*) Bard, P.: Some Postural Deficiencies Following Certain Cortical Ablations, Am. J. Physiol. **97**:503 (June) 1931; (*b*) The Cortical Representation of Certain Postural Reactions and the Normal Functioning of Cortical Remnants, J. Nerv. & Ment. Dis. **76**:56 (July) 1932; Arch. Neurol. & Psychiat. **28**:745 (Sept.) 1932. (*c*) Bard, P.; Brooks, C. M., and Lowry, T.: Cerebral Localization of "Hopping" and "Placing" Reactions in Cats, Rats and Alligators, Am. J. Physiol. **101**:3 (June) 1932.

had settled into a crouch. A common cause of the crossed pose of the forelegs was a prematurely arrested act of turning. These weird postures, all due to deficient ability to place the feet in the proper position, were sometimes maintained for astonishingly long periods.

These observations on decorticate cats in the chronic condition are by no means original. Dusser de Barenne [1] stated that when abnormal positions of the feet were imposed on either of his decorticate cats they were corrected less rapidly and less completely than in normal animals, and he also described the slow sliding of the feet into peculiar positions without the usual corrective response. Schaltenbrand and Cobb,[2] who studied a cat without neocortex during a survival period of five months, mentioned that "sometimes the forelegs crossed by mistake and the animal tried in vain to bring them into the right position."

In general, such abnormalities have been attributed to a deficiency in sensibility, usually to some disturbance of the proprioceptive mechanism. But with the appearance of Rademaker's analyses [3] of the act of standing it became apparent [4] that the trouble had its basis, to a large extent at least, in an absence or a deficiency of certain reactions which that investigator has described and shown to be among the many factors which make possible normal standing. These are: (*a*) placing reactions (manifestations of *Stehbereitschaft*), which he found to be wholly absent after complete decortication and absent in the contralateral legs after removal of one entire hemisphere, and (*b*) hopping reactions (*Hinkebeinreaktionen; réactions du saut à cloche pied*), which, according to Rademaker, merely become retarded and hypermetric in dogs after decortication.

THE PROBLEM

The present investigation of the placing and hopping reactions had its origin in an attempt to account for the attitudinal peculiarities of the decorticate animals. But at an early juncture the observation was made that cats lacking certain small cortical areas showed disturbances of these reactions as great as those exhibited by the wholly decorticate animals. At the same time it was noticed that the responses were not in the least impaired by the extirpation of other more extensive areas.

1. Dusser de Barenne, J. G.: Recherches expérimentales sur les fonctions du système nerveux central, faites en particulier sur deux chats dont le néopallium avait été enlevé, Arch. néerl. de physiol. **4**:31, 1919.

2. Schaltenbrand, G., and Cobb, S.: Clinical and Anatomical Studies on Two Cats Without Neocortex, Brain **53**:449, 1931.

3. Rademaker, G. G. J.: (*a*) On the Physiology of Reflex-Standing, Proc. koninkl. Akad. v. Wettenschappen te Amsterdam, 1927, p. 796; (*b*) Expériences sur la physiologie du cervelet, Rev. neurol. **36**:338 (March) 1930; (*c*) Das Stehen, Berlin, Julius Springer, 1931.

4. Bard, P.: Am. J. Physiol. **97**:503 (June) 1931.

These early experiences with animals that had been prepared for other purposes indicated not only that the placing and hopping reactions are under the control of the cerebral cortex, but that their representation there has a definite localization. The simplicity of these reactions, their uniform presence in normal cats and their easy elicitation by specific postural stimuli recommended them as singularly favorable instruments for the study and delimitation of the central control.

THE PLACING AND HOPPING REACTIONS OF NORMAL CATS

Placing Reactions.—In this report only five of seven placing reactions evokable in cats will be considered. It can be stated explicitly that each of these is wholly independent of vision, for each remains unmodified after blindfolding or enucleation of the eyes. The five placing reactions are as follows:

1. If a cat is held in the air with the legs free and dependent and with the head held up (so that it cannot see its forefeet or any object below and in front), the slightest contact of the backs of either pair of feet with the edge of a table results in an immediate and accurate placing of the feet, soles down, on the table close to its edge.

2. If the forelegs of a cat suspended in the air are held down, and the chin is brought in contact with the edge of a table, both forefeet on being released are instantly raised and placed beside the jaws. Usually this is followed by extension, so that a standing position is quickly assumed. If a blinded animal is used, the forefeet, even though not held down, remain hanging until the chin touches the table.

3. If the forelegs or hindlegs of a cat that is standing, sitting or crouching on a table are thrust over the edge, they are immediately lifted so that the feet quickly regain their original positions on the table.

4. If any leg of a standing cat is passively abducted without being held, it is at once adducted and lowered so as to restore the foot to its normal standing position.

5. Although each of the foregoing reactions may be adequately studied in animals with vision intact, this final one can be evoked in pure form only after blindfolding, enucleation of the eyes or removal of the visual cortex. The animal held in the air with the forelegs free is moved toward some solid object. As soon as the tips of the vibrissae of one or both sides touch the object, both forefeet are accurately placed on it. Unless the influence of the eyes is excluded, a visual placing reaction of the forelegs will be evoked under these circumstances.

The first three reactions have been described by Rademaker,[3c] for the most part in dogs, and they are evoked, as he pointed out, by stimuli emanating from the surface of the body. It is possible, however, that a proprioceptive element may enter into the second and third. The fourth and fifth are proprioceptive and tactile responses respectively. All are rapid and precise, and have as their common object the placing of the feet in just the right position for standing. In my experience these reactions are executed with greater ease and accuracy in cats than in dogs. The cat does not show to any appreciable extent another placing reaction which Rademaker has found in the dog: the putting down of the hindfeet when the tip of the tail touches a supporting surface as the animal is being lowered through the air. The visual placing reaction is well developed in cats. It

occurs when the head of the animal approaches a table top or the floor, and it consists in a forward movement of the forelegs on the shoulders together with slight flexion at the elbows and marked dorsiflexion at the distal joints with spreading of the toes. Since in unpublished work Orias and I have found that this response has a neural basis which differs from that of the five placing reactions listed, the description of its cortical management together with that of a very similar cortical reaction of labyrinthine origin will be presented in a separate communication.

Hopping Reactions.—These are essentially corrective movements of the legs which serve to maintain a standing posture under conditions involving displacement of the body in the horizontal plane. They are most satisfactorily demonstrated by holding the animal so that it stands on one leg. Then on movement of the body forward, backward or to either side the leg hops in the direction of the displacement so that the foot is kept directly under the shoulder or hip. This the normal cat does with accuracy and rapidity. Rademaker [3] showed that a disappearance of the supporting tone of the leg is an integral part of each hopping reaction. With the leg in the median standing position the positive supporting reaction is strong, and the leg is acting effectively as a rigid pillar, but with any displacement of the body that induces a deviation from the median position the supporting tone diminishes, and the foot is raised, transposed in the direction of the displacement and put down again to give a median support for the body in its new position. The suggestion that these reactions are caused by stretching one or another group of muscles, i. e., that they are myotatic in origin, is a reasonable one. Recently Rademaker and Hoogerwerf [5] brought forward some evidence that this is actually the case.

In the cat the hopping reactions of the forelegs are more perfect than those of the hindlegs. In each leg the response to adduction is usually the best developed. The hopping reactions, like the placing reactions, are essentially corrective movements of the legs. They, too, are concerned in putting the feet in the normal standing position, but, in addition, they contribute to the maintenance of equilibrium.

EXPERIMENTAL METHODS

Since a detailed report of any extensive surgical procedure is of little real aid to the reader who may wish to acquire or criticize the technic, the following comment will be confined to a brief general description of how the purpose of these operations was attained. It may be of some service to point out that an experience embracing more than three hundred and fifty operations on the brain of the cat has indicated three general requirements for anything approaching sustained success in this sort of work.

1. Scrupulous regard for the cardinal principles: rigid asepsis, avoidance of trauma to tissues, permanent hemostasis and careful closure.

2. Choice of Anesthetic: The use of ether gives a "wet," bulky, profusely bleeding brain and should be avoided. Certain members of the barbituric acid group offer the greatest advantages, and three of these, administered by the intraperitoneal route, have been employed in the present work: sodium barbital (6 cc. of a 5 per cent solution per kilogram of body weight); *di*-allyl-barbituric acid in

5. Rademaker, G. G. J., and Hoogerwerf, S.: Réactions provoquées par l'allongement passif du muscle semi-tendineux, Arch. néerl. de physiol. **15**:338, 1930.

the form of dial (0.65 cc. per kilogram); and sodium-ethyl-1-methyl-butyl barbiturate, supplied as pentobarbital sodium (0.75 cc. per kilogram). In dial and pentobarbital sodium the investigator possesses two agents which greatly facilitate the course of intracranial procedures. With sufficient dosage one may expose with minimal hemorrhage a somewhat shrunken brain which on incision and dissection bleeds surprisingly little.

3. Careful Postoperative Management: No amount of operative skill can avert the disaster which is likely to follow inadequate postoperative nursing. Maintenance of a body temperature within the normal range (from 37.8 to 39 C. [100 to 102.2 F.]) is important during the hours when the ability to regulate it is depressed by the anesthetic. If hemorrhage has been considerable, an intraperitoneal or a subcutaneous injection of saline solution (about 100 cc. for a cat weighing 3 Kg.) will aid in the restoration of the volume of blood. Furthermore, administration of fluid induces a more rapid recovery from the action of any nonvolatile anesthetic. After certain cerebral ablations, especially those involving damage to the olfactory mechanism, some cats refuse to eat spontaneously for many days. Such animals must be patiently fed by spoon and pipet until they begin eating and drinking of their own accord.

The cranial cavity has always been approached through a wide defect in the bone lying beneath the temporal muscle. The latter is incised and reflected in such a way as to permit its being used to close tightly the opening in the skull. The rapid postoperative growth of a tough, inelastic "false dura," under which the leptomeninges become organized, assures a complete separation of the muscle from the cranial contents. Although at least a part of the dura of the side operated on invariably shows at autopsy a marked thickening, no growth of scar tissue into cerebral tissue has ever been encountered. None of the animals has had postoperative convulsions or other signs of cerebral irritation. The temporoparietal approach used in this work gives direct access to all parts of one neocortex except its medial surface and the longitudinal, frontal and sigmoid gyri. But it allows removal of the sigmoid gyri along with the frontal and a little of the coronal gyrus. To approach these areas directly one must open the frontal sinus and be content with a limited exposure and an imperfect closure. Postoperative herniation of cerebral tissue frequently occurs under these conditions, and as a result this particular approach has been discarded. In the cat, suturing the dura is difficult and wholly unnecessary. The actual removal of cerebral tissue has been effected by incision with a small sharp knife followed by careful dissection with a flat, narrow spatula. Experience has indicated that unless the ablations are small or confined to the caudal parts of the cortex it is wiser to perform bilateral removals in two stages.

In many of the experiments to be described the anatomic determination of the presence or absence of the motor cortex was supplemented by exploration with a stimulating current just before killing the animal. This was done with bipolar electrodes connected with the secondary of a Harvard inductorium. The stimulation was always carried out under light dial anesthesia (0.5 cc. per kilogram). As pointed out by Fulton, Liddell and Rioch,[6] this anesthetic has the property of leaving remarkably intact the excitability of the motor cortex.

In every case the brain was removed at autopsy. After fixation the extent of the ablation was determined as exactly as careful gross inspection allowed. The brains of several animals used in this investigation were sectioned and studied

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6. Fulton, J. F.; Liddell, E. G. T., and Rioch, D. McK.: "Dial" as a Surgical Anaesthetic for Neurological Operations; With Observations on the Nature of Its Action, J. Pharmacol. & Exper. Therap. **40**:423, 1930.

histologically by Dr. D. McK. Rioch of the Department of Anatomy, Harvard Medical School, who provided me with the reports of his observations. These sectioned brains were from animals which were the subjects of another neurophysiologic investigation carried on in collaboration with Dr. Rioch.

EXPERIMENTAL RESULTS

Equivalence of Complete Decortication and Removal of Both Frontal Poles.—One decorticate cat (103) was killed two years and four months after the second and final cerebral operation. A preliminary study of serial sections (Weigert-Pal) by Dr. Rioch revealed the following facts about this brain:

The neocortex had been completely removed on both sides. A considerable part of archicortex and paleocortex had been extirpated or damaged, especially on the left side. The medial basal olfactory area remained intact on both sides and showed fiber connections with the remaining portion of the olfactory bulbs. The pyriform lobe and amygdala were almost wholly intact on the right side, but had been replaced by a large cyst on the left. The hippocampus had been removed on the left, and on the right there remained only a degenerated fragment of this structure. In the striatum the parts spared were the caudomedial portion of both caudate nuclei, most of each putamen and all of the globus pallidus and entopeduncular nucleus on each side. The ansa lenticularis, fields of Forel, nucleus subthalamicus, zona incerta, substantia nigra and red nucleus appeared bilaterally normal. The lateral portions of the dorsal thalami had been ablated, but the periventricular system and the medial portions of the anterior, medial and ventral groups of nuclei were left. The medial and lateral preoptic and hypothalamic areas were intact. Although the descending columns of the fornix were absent, and there was a reduction in the size of the bundle of Vicq d'Azyr, the fibers of which could not be followed into the anterior thalamus, the tegmental connections of this region were apparently normal. Also the habenular ganglia and the habenulopeduncular tracts remained. The optic nerves and chiasm had a normal appearance, and although the optic tracts did not seem reduced in size, both lateral geniculate bodies had been damaged laterally. The medial geniculate bodies were normal. Except for degeneration of the peduncles and pyramids and a reduction in the size of the superior colliculi and the pontile nuclei, the mesencephalon and rhombencephalon were unaffected.

Cat 313 succumbed to an acute pulmonary infection six weeks after a second intracranial operation. The survival period up to the second day preceding death was marked by excellent health and a functional condition which showed but little modification after the tenth day. Gross examination of the brain disclosed a condition which accorded with the notes made at the two operations. The entire neocortex of both sides had been removed. The olfactory portion of the brain, with the exception of the olfactory bulbs and the rostral part of each stalk, had been largely spared. The lesion had involved the caudate nuclei laterally and rostrally, but the rest of the striatum, the body of the dorsal thalamus, the hypothalamus and the midbrain apparently were not involved in the operative removal.

It is of course hazardous to venture an opinion as to the precise extent of the ablations which were carried out in the two decorticate animals still alive. But on the basis of careful operative notes it can be said with fair assurance that in cats 228 and 244 all the cerebral cortex and most, if not all, of the substance of the corpora striata were removed. It is probable that in cat 244 the thalami were left intact except for small rostral invasions made in removing the caudate nuclei. But in cat 228 the lateral parts of the diencephalon were intentionally cut away. At the time of writing (December, 1932), cat 228 is in the thirteenth, and cat 244 in the sixth, month of survival. Each has exhibited persistent good health and a practically constant clinical picture.

The general symptoms and behavior of these four decorticate cats will not be described in this report. For the present purposes it is

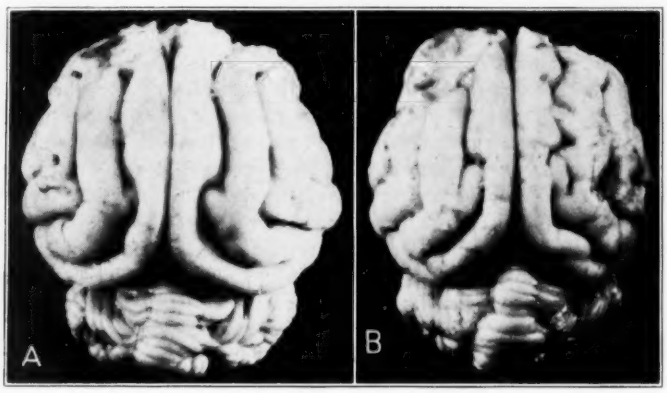

Fig. 1.—The brains of cats 304 (*A*) and 298 (*B*).

essential to say only that each has shown a permanent complete absence of the placing reactions and marked disturbances of the hopping reactions.

Although closely resembling normal cats in their general behavior, three animals without frontal poles proved to be just as deficient as regards the placing and hopping reactions as the cats lacking neocortex or all cortex. These were cats 121, 298 and 304, which were kept sixteen, three and two months respectively after removal of the second frontal pole. There can be no doubt that these animals represent chronic experiments. Each showed a constant degree of deficiency during the period between its recovery from the immediate effects of the operation and its termination. The case histories indicate not the slightest capacity to regain the placing reactions or to improve those hopping reactions which were not entirely lost.

The brains of cats 298 and 304 are shown in figure 1. In 298 the ablation involved on both sides the frontal extremity of the longitudinal (marginal) gyrus, the anterior and posterior sigmoid gyri and the gyrus proreus (orbital or frontal gyrus). On the right side the anterior half of the coronal gyrus had been removed, and on the left the ablation had included the most anterior portion of the suprasylvian gyrus, but had spared the coronal gyrus. The somewhat ragged appearance of the convexities of the hemispheres is due to the fact that the dura was adherent to the pia-arachnoid in certain places, and in removing the

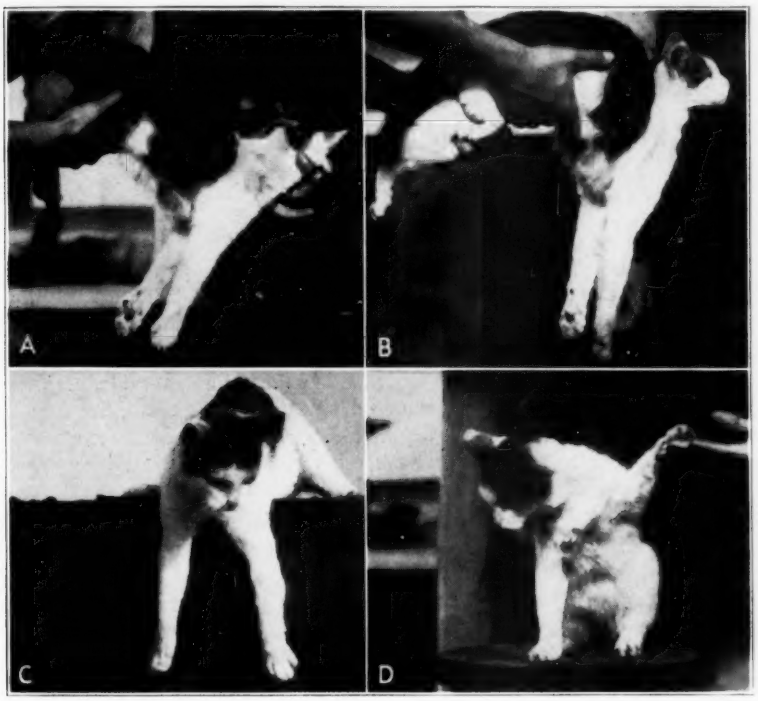

Fig. 2.—Photographs of cat 298 taken three months after removal of the second frontal pole. The bilateral failure of three placing reactions is shown in *A*, *B* and *C*. The reaction the absence of which in the left foreleg is indicated in *D* was equally defective in all four legs. Precisely the same deficiencies were present in cats 121 and 304 and in the four decorticate animals (103, 228, 244 and 313).

former at autopsy some superficial stripping of the cortex could not be avoided. In cat 304 the orbital, both sigmoid and the coronal gyri of both sides were wholly removed. On the left side the ablation extended slightly more caudad and involved the rostral extremity of the longitudinal and suprasylvian gyri. It is unfortunate that satisfactory photo-

graphs of the brain of cat 121 are not available. On Jan. 6, 1930, a portion of the left frontal pole, including the sigmoid, coronal and a small bit of the anterior ectosylvian gyri, was ablated. On March 18, in a second operation, all the cortex of the right hemisphere lying rostrad to the level of the sylvian fissure was removed, and some damage was done the right caudate nucleus. The animal was killed on Aug. 6, 1931, more than sixteen months after the second operation. Throughout this time the cat remained in perfect health, and constantly exhibited, in spite of the inequality of the two extirpations, bilaterally equal deficiencies in the placing and hopping reactions precisely like those of the six animals already mentioned.

The disturbances in these reactions were the same in the four decorticate animals and in the three without frontal poles. The following description applies uniformly to the seven animals throughout their periods of survival. Figure 2 illustrates the absence of four placing reactions in cat 298. Taking the five placing reactions in order, the disturbances are as follows:

1. If, with legs hanging freely down, the body is moved so that the backs of either pair of feet are touched or even pressed against the edge of a table, placing of the feet does not occur. Even after forward displacement of the body has induced a considerable degree of retroflexion of the legs at hip or shoulder no response occurs (fig. 2 *A*). But finally, after further retroflexion, the foot is lifted, carried forward and placed clumsily, sometimes back down, far inside the table edge. This is a reaction which Rademaker[3e] termed a proprioceptive correcting movement. In origin and execution it is quite distinct from the delicately accurate response to light contact of the dorsal surface of the foot or leg, which is the true placing reaction and which is invariably exhibited by the normal animal.

2. When the cat is placed with the chin resting on the edge of a table the forefeet are not brought up and put beside the jaws. Instead they remain down for any length of time that the animal is held in this position (fig. 2 *B*). If, as is usually the case with a decorticate preparation, the cat remains quiet, the legs are held motionless, rigidly extended. If, as often happens when only the frontal poles have been removed, the animal becomes restless, the forelegs may spasmodically excute pawing or running movements, coupled sometimes with vigorous general struggling, but in spite of flexion at the elbow and shoulder the feet are not brought up onto the edge of the table.

3. With forelegs or hindlegs thrust over the edge of a table the animal is unable to raise the feet and therefore cannot regain its original position on the table. Provided the surface is not so smooth that the weight of the dependent parts causes the body to slide and fall, any one of these animals would remain indefinitely in the position shown in figure 2 *C*. When thus dependent, the forelegs are rigidly extended and do not move. By throwing its head back and simultaneously lifting the body on the hindlegs, each of these cats occasionally managed to get one foreleg, and later the other, back on the table. But in these rare instances the forelegs did not actively participate in the movement; they were only passively lifted in the elevation of the forepart of the body. When the hind-

legs are placed over the edge of a table, they may remain quietly dependent in extension or moderate flexion, and though they may make alternate stepping movements it is seldom that they are lifted sufficiently to place the feet. When this occurs it is always accomplished by dragging the hindlegs up in a forward scrambling movement of the forelegs.

4. If any leg of one of these cats is passively abducted to a horizontal position with the foot resting on some supporting object, the leg remains in this awkward attitude almost indefinitely. The attitude is broken only when locomotion or sudden turning sets in, with consequent participation of the leg in the stepping.

5. Wholly decorticate cats lack the visual placing reaction of the forelegs, whereas cats without frontal poles retain this response. Bringing the vibrissae of the former into contact with a supporting surface does not induce placing of the feet. Nor does this evoke placing in the case of the cats lacking frontal poles, provided they are blindfolded or blinded. With eyes active, they always place the forefeet before the vibrissae have made the contact.

Rademaker [36] found that in the dog complete unilateral decortication leads only to some retardation and a slight hypermetria of the hopping reactions of the contralateral legs, and that these modifications are bilateral after complete decortication. A personal study of three unilaterally decorticate dogs and of one dog lacking the neocortex of both sides has, on the whole, confirmed Rademaker's more extensive canine observations. But in cats the disturbances of the hopping reactions are much more profound than in dogs. Again, as great an effect is produced by bilateral removal of the frontal poles as by complete decortication. To represent the disturbances graphically requires a moving picture, and although cinematographic records of nearly every cat have been made, it hardly seems worth while to publish the long strips which would be necessary for adequate illustration. Therefore the following description of the equally deficient reactions shown by the seven cats under consideration must suffice:

When the animal is held so that it stands on either foreleg, no hopping occurs on moving the body backward; the foot is merely dragged over the floor. In the case of the hindlegs this displacement usually evokes a retarded, weak and hypometric backward stepping. When lateral displacement induces abduction of a leg, a tendency to hop is only occasionally seen, and then the reaction is weak, the foot is scarcely lifted, and the movement is not repeated sufficiently rapidly to keep pace with even slow displacements of the body. When lateral displacement causes adduction, a better response is usually evoked, but in all tests it fails with further displacement and the animal allows itself to go over on hip or shoulder. When this reaction does occur it is hypometric and retarded; i. e., it begins after a greater degree of adduction than normally suffices to evoke it. The best hopping reaction found in these animals is that obtained with forward displacement, but it is always retarded and jerky.

Deficiencies Following Unilateral Operations With Evidence that the Cortical Control Is Entirely Crossed.—The five placing reactions and the hopping reactions have been studied in a series of seventeen cats subjected to operations that were confined to one side of the cere-

brum and in which the least extensive ablation was unilateral removal of all neocortex. Except for two animals which were kept only five and seven weeks, the periods of survival have varied from two months to three years. Five animals were killed in the third, three in the fourth, two in the fifth, one in the ninth and one in the tenth postoperative month. Three animals, still alive, have survived four months, two years and three years respectively. In this series it happens that there is no correlation between the extent of cerebral removal and the length of survival. The ablations the limits of which have been determined at autopsy have varied from removal of all neocortex, with only small involvement of other cerebral tissue (four animals), to extirpation of all cerebral structures situated lateral, dorsal and rostral to the hypothalamus (ten animals). Serial sections of four brains have been studied. For the purposes of this report there is no need to give in

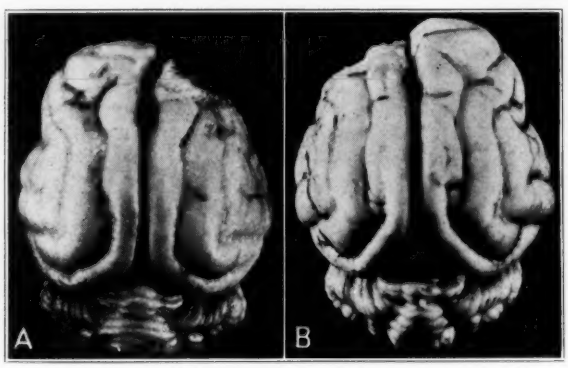

Fig. 3.—The brains of cats 194 (*A*) and 302 (*B*).

detail the precise limits of these ablations. The important point is that in spite of large differences in magnitude they have produced the same deficiencies of the reactions. In short, whether one removes on one side merely the neocortex or all the tissue above the hypothalamus there result in the contralateral legs the same permanent disturbances of the placing and hopping reactions as are found in all four legs after bilateral decortication. After recovery from the anesthesia and the immediate effects of the operation these seventeen cats showed no trace of any disturbance in the reactions of the ipsilateral limbs. It is quite certain that the cortical control is wholly contralateral.

As regards the localization of this control, much interest attaches to the fact that when only the frontal pole of one cerebral cortex is removed the same permanent contralateral disturbances are produced as after complete unilateral decortication. Again, there are no ipsilateral effects. Operations restricted to one frontal pole have been performed in eight cats. Figure 3 shows the brains of two of these animals, cats

194 and 302. In cat 194 the operation was on the right side, and inspection shows that the ablation was confined to a removal of the gyrus proreus, the anterior and posterior sigmoid gyri and the anterior half of the coronal gyrus. In the left hemisphere of cat 302 the extirpation proved to be the same, except that it spared a small margin of the posterior sigmoid gyrus lying between the arms of the ansate sulcus, and extended in a narrow strip backward across the posterior half of the coronal gyrus. In the other six animals the ablations varied from these in extent only by 2 or 3 mm. Just before they were killed, four of these cats were anesthetized with dial and both cortices explored with

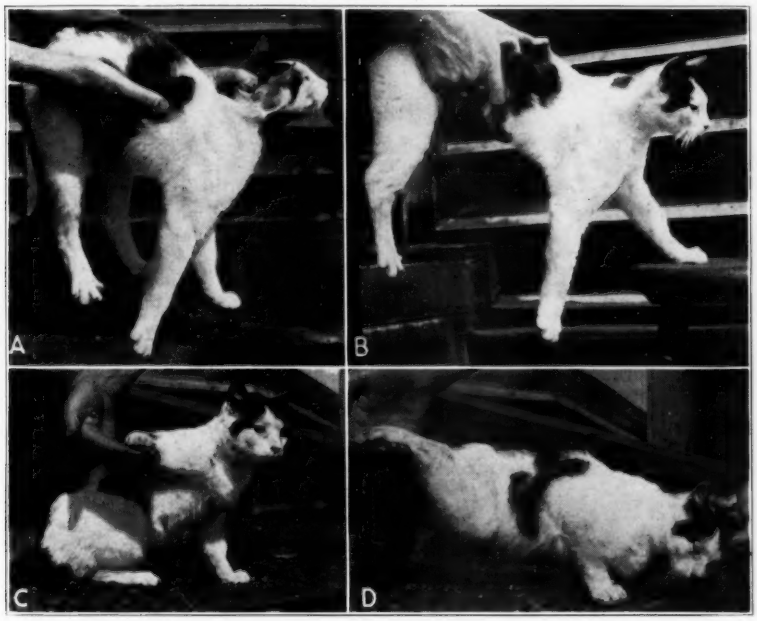

Fig. 4.—Photographs of cat 302. The presence of two normal placing reactions in the left foreleg and their failure in the right foreleg are shown in *A* and *B*. The absence of another placing reaction of the right legs is illustrated in *C* and *D*. The left frontal pole had been ablated (fig. 3 *B*).

stimulating electrodes. In every case the usual movements of the contralateral legs were obtained from the sigmoid gyri of the intact hemisphere, but in no instance were such movements obtained from the side operated on, even when currents which were so strong that they spread to the opposite cortex were used. This fact is of course correlated with the absence of the motor areas for the legs. In each cat, however, movements of the contralateral ear were obtained with minimal strengths of current from the cortex of the side operated on. The excitable area yielding movements of the ear lies, in the majority of cats, at the point

where the coronal gyrus joins the suprasylvian gyrus. Although this area lay just behind the margin of the extirpation it was normally excitable in all the animals tested. These observations indicate that the cortex remaining was not damaged.

Four photographs of cat 302 are shown in figure 4, which illustrates the failure of the placing reactions in the legs opposite the extirpated frontal pole and at the same time indicates their presence in the legs contralateral to the intact cortex. This figure also represents the condition of the placing reactions in all seventeen animals unilaterally operated on and lacking neocortex or more. With the eight cats without one frontal pole, they constitute a group of twenty-five, homogeneous as regards these postural reactions. In such preparations the reactions of the legs of the unaffected side serve as controls for those of the opposite side, and it is therefore possible in one and the same animal to compare and contrast normally reacting legs with legs that have a maximal deficiency. When with vision excluded the backs of the feet are brought into contact with the edge of some supporting surface, the foot opposite the intact hemisphere is instantly lifted, put forward and placed, whereas the foot of the affected side remains with the dorsum against the edge (fig. 4 *A*). Only when forward displacement of the body has considerably retroflexed this leg on the proximal joint does it move forward in what is apparently a proprioceptive correcting movement which places the foot far inside the edge. When the chin of one of these unilaterally deficient cats is allowed to rest on the edge of a table, release of the forelegs is instantly followed by placement of the foot of the unaffected side beside the jaw, but although this leg may at once assume a standing position, its fellow remains extended with foot hanging down parallel to the edge (fig. 4 *B*); it is put forward only if the animal starts to walk or struggle. When either pair of legs is thrust over the edge of some supporting surface the normal leg is at once raised to bring the foot back on the table, and the other remains helplessly down until in turning or stepping backward the cat passively restores it to its normal attitude. Unless they are very restless and show a strong tendency to move about, such animals allow the feet contralateral to the ablation to remain on one's hand or another object after passive abduction (fig. 4 *C* and *D*), but the opposite legs are immediately restored to the standing or crouching position after such manipulation. The placing which occurs after exclusion of vision on bringing the vibrissae into contact with some solid object is confined to the foreleg opposite the intact cortex, and is evoked only by stimulation of the vibrissae of that side.

In this group of cats the disturbances of the hopping reactions were confined to the legs contralateral to the cerebral lesion. Their defi-

ciencies were similar to those produced in the legs of both sides by bilateral extirpation of all the cortex or of both frontal poles.

Cat 194 was killed fourteen weeks after operation, and cat 302 lived seven weeks before it was killed. The periods of survival of the other animals in this group were three, four, five, six, seven and nine weeks. After recovery from the immediate effects of the operation, none showed any change in the placing and hopping reactions. On the side of the operation they remained normal; on the other side the deficiencies were maintained without any sign of improvement.

Bilaterally Equal Deficiencies Produced by Complete Decortication on One Side and Removal of Only the Frontal Pole on the Other Side.—The evidence presented in the foregoing section has shown: (1) that a cat without one frontal pole is, in respect to the placing and hopping reactions, as deficient as a cat lacking one entire hemisphere, and (2) that the deficiencies following an effective unilateral operation are always confined to the legs of the side opposite the ablation. On the basis of the second of these facts it became possible to make a further and even more conclusive test of the functional equivalence of the two types of ablation. This was done by preparing two animals in which removal of one hemisphere was combined with extirpation of the frontal pole of the other.

In cat 168 an attempt was made on Nov. 18, 1930, to remove the entire cerebral cortex and striatum on the left side. Following this operation the right legs showed a permanent absence of the placing reactions and the characteristic deficiencies of the hopping reactions already described. In a second operation, carried out on June 10, 1931, the frontal pole of the right cortex was removed. A rapid and uneventful recovery ensued. The reactions of the left legs, which had been unaffected by the first operation, now presented deficiencies as great as those of the right legs, and during the seven and a half months which elapsed before the animal was killed, on Jan. 28, 1932, the deficiencies remained equal on the two sides. Gross study of the brain revealed on the right side an extirpation of the orbital and both sigmoid gyri with removal of the anterior margin of the coronal gyrus and the forward tip of the longitudinal gyrus. Dr. Rioch's preliminary study of serial sections of this brain showed that the object of the two operations had been attained. Although the motor cortex had been removed on the right side, the ventricle had not been opened, and the rest of the cortex appeared normal. On the left side, all cortex except the caudomedial third of the pyriform lobe and the medial portion of the amygdaloid complex had been removed. Practically all of the left striatum had also been cut away.

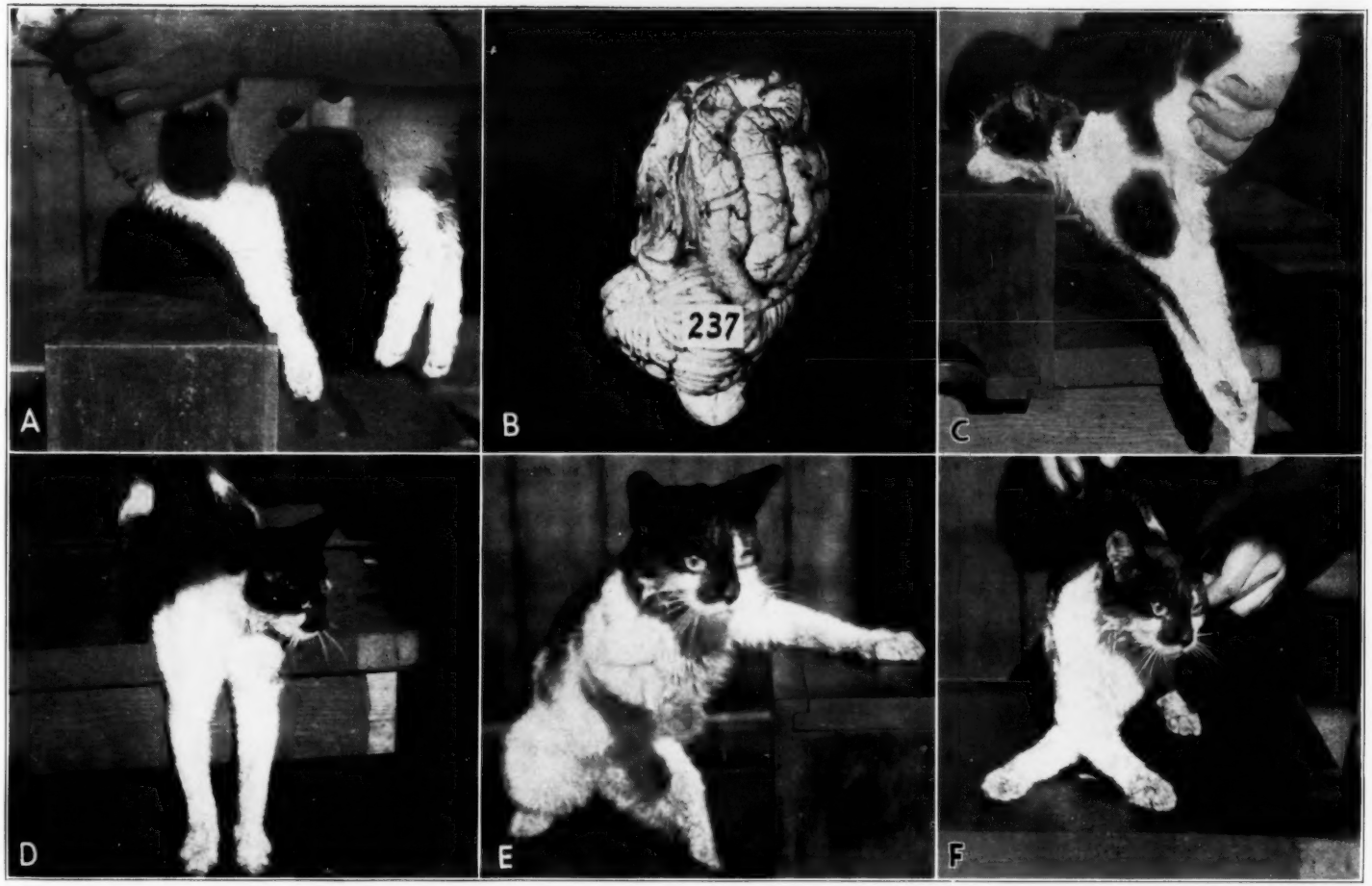

Fig. 5.—Photographs of cat *237*. *B* indicates the extent of the bilaterally unequal cerebral ablations which were performed in a single operation. *A*, *C* and *D* show the permanent, bilaterally equal deficiencies of three placing reactions. The inability to restore an abducted leg to the normal standing position, a defect which was present to an equal extent in all four legs, is shown in *E*. *F* illustrates one of the

In cat 237 a similar asymmetrical ablation was performed. In this case, however, it was carried out in one stage. After removal of a large part of the left hemisphere through a left parietotemporal defect, the falx was incised anteriorly, and the frontal pole of the right cortex was cut away. The animal made a satisfactory recovery and remained in excellent condition during a survival period of six and a half months. The bilateral absence of the placing reactions is shown in figure 5, and repeated examinations revealed the same deficiencies of the hopping reactions as were encountered in the wholly decorticate cats, in the three cats without frontal poles and in cat 168. As in cat 168, the reactions of the legs opposite the remaining cerebral cortex showed not the slightest tendency to return or improve. It is reasonable to suppose that if any improvement could take place after such operations it would have shown itself within the long periods of survival of these two animals.

Figure 5 also shows a dorsal view of the brain of cat 237. It is evident that the amount of tissue removed from the right frontal pole was less than in the case of cat 168. Inspection shows that a clean slice cut away all tissue in front of a line passing parallel to, and at least 2 mm. behind, the cruciate sulcus. A good idea of the extent of this ablation can be obtained by comparing this brain with that of cat 302, shown in figure 3. The gyrus proreus, the anterior sigmoid gyrus and the rostral half of the posterior sigmoid gyrus have been removed. It is obvious that on the left side the operative removal had extensively involved the brain stem. In fact the intention at operation was to remove above the mesencephalon all the cerebrum except the hypothalamus. This brain was also sectioned, and the summary of Dr. Rioch's report follows:

> On the right side the entire remaining cortex was normal except for a glial reaction in the part immediately bordering the ablation.
>
> The sections showed on the left side a complete absence of all cortex, striatum and geniculate bodies. In the dorsal thalamus the only remaining portions were the periventricular system, a few cells of the commissural nuclei and possibly a few cells belonging to the median portion of the nucleus ventralis, all of which showed glial proliferation. Only the caudal halves of the habenular ganglia and a portion of the habenulopeduncular tract remained intact.
>
> The hypothalamic region had been spared, but showed a widespread glial reaction; many of the cell groups showed crowding of their elements, and some groups were smaller than on the right side. The same could be said of the subthalamus. The lesion passed just lateral to the red nucleus and involved the lateral part of the substantia nigra and the reticular substance of the mesencephalon. Both colliculi had been damaged, and a glial reaction extended to the central gray matter around the aqueduct.

Although no test of the electrical excitalibity of the remaining part of the right cortex was made in cat 168, it is clear that the motor areas

Fig. 5.—Photographs of cat 237. *B* indicates the extent of the ablation. *A*, *C* and *D* show the permanent, bilaterally equal deficiencies of three placing reactions. The inability to restore an abducted leg to the normal standing position, a defect which was present to an equal extent in all four legs, is shown in *D*. In *A* illustrates one of the

for the left legs were removed in toto. In cat 237 the foreleg motor area, situated on the anterior sigmoid gyrus, had been cut away, but there might be some question as to the presence of the hindleg area, which is located on the posterior sigmoid gyrus. The caudal portion of this gyrus was spared. But this was the site of a considerable glial reaction and might have been functionless. Further light was obtained on this question when just before the cat was killed the remaining cortex was explored with electrodes under light dial anesthesia. Brisk movements of the left ear were induced when currents of minimal strength were applied at the rostral extremity of the suprasylvian gyrus just behind the lateral arm of the ansate sulcus. But the application of the electrodes to all other parts of the convexity of the right hemisphere failed to give any motor effect. Persistent attempts to evoke contralateral movements of the limbs from the tissue lying between the cut surface and the ansate and coronal sulci failed even when the strength of the stimulating current was such as to spread to the musculature of the right side of the head. Finally toward the end of the experiment a small quick jerk of both left legs was evoked from the upper medial surface of the cortex bordering on the ablation. But this resulted only when currents of maximal strength were used. At the same time that this result was obtained, the excitability of the ear area had not diminished. It is questionable whether this result can be interpreted as evidence that a small part of the motor area for the left legs had been left. It is not impossible that the movements were produced by a spread to some subcortical structure.

It has been stated that as regards the placing and hopping reactions, cats 168 and 237 were identical with the wholly decorticate animals. And in other ways they showed decorticate characteristics. They had the same tendency to assume abnormal attitudes of the legs; an example of this is shown in figure 5 *F*. The sensibility of the feet to pinching was markedly and equally depressed on both sides. Both animals showed an item of behavior which was characteristic of all four decorticate cats, namely, exaggerated postprandial chop and nose licking with head dorsiflexed. But in other respects they differed in striking fashion from the cats without cortex. The curiosity and the inane desire to seek and maintain human companionship which were displayed by cat 237 were beyond anything of the kind I have ever seen in a normal cat. Unlike their decorticate companions both cats were able to find and devour their food as readily as normal cats, and they gave unmistakable evidence of recognizing the preparations which daily signaled its coming. So far as could be determined, the right eye in both cats was nearly completely blind, but vision in the left seemed normal. Cat 237 would invariably go to any object moving in his left visual field or try by proper orientation to bring the source of a sound into this field.

Absence of Deficiencies Following Extensive Postfrontal Ablations of the Cortex.—In attempts to demonstrate the localization of any given function in the cerebral cortex it is not enough to show, however conclusively, that that function is regularly and permanently made deficient or abolished by the extirpation of a specific region. There always remains the possibility that remaining areas normally make important contributions to the function of the region the removal of which has produced the defect. In order to conclude that a cortical function has its sole residence in a restricted area it is also necessary to demonstrate that the function is not in the least affected by removal of all cortex except this area. This has been done in the case of the cortical control of the placing and hopping reactions.

Early in the course of this work it was observed that several cats without one occipital pole and other cats from which one temporal region

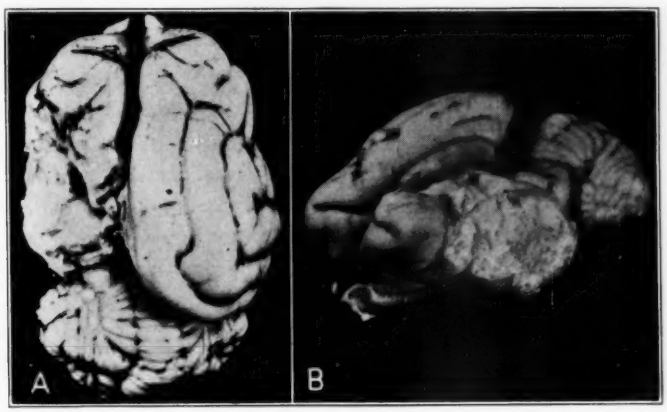

Fig. 6.—The brain of cat 296, which possessed normal placing and hopping reactions in all four legs, is shown in *A*. In spite of the extensive ablation of the left cortex in the brain of cat 241, shown in *B*, the reactions of the right foreleg were normal and matched, in every respect, those of the left foreleg controlled from the intact right hemisphere.

had been removed did not show, in any phase of long periods of survival, the slightest disturbance of the postural reactions of the legs. Even removal of all cortex behind the level of the sylvian fissure on both sides left them wholly normal. These observations and the force of the reasoning set down in the last paragraph led to a systematic attempt to determine how much cortex could be removed on one side without disturbing the reactions of the opposite legs. Because of the fact that the motor areas for the legs had been removed in every animal that had shown deficiencies it seemed reasonable in this endeavor to remove all cortex situated caudal to this region. Altogether eight cats

of this type were prepared and studied. Observations made on three animals that retained of the left neocortex only the gyrus proreus, the sigmoid gyri, a small part of the coronal gyrus and the most rostral portion of the longitudinal gyrus showed conclusively that this fraction can manage the reactions as well as the entire cortex.

Figure 6 *A* shows the brain of one of these animals, cat 296. In cats 209 and 352 the ablation and the clinical findings were exactly the same as in this animal. Following emergence from the anesthetic each showed some depression of the placing and hopping reactions of the right legs. But within a week the reactions on this side had become normal and indistinguishable from those of the left legs which, being under the control of the intact right hemisphere, were precisely like those of vigorous control cats which had not undergone an operation. With these may be included cat 236 the cortical remnant of which included, in addition to the areas which remained in 296, 209 and 352, the rostral two thirds of the longitudinal gyrus and a small fraction of the adjacent suprasylvian gyrus. In it the reactions continued to be quite normal in all four legs.

In three animals of this group (cats 205, 290 and 305) essentially the same ablation was performed as in 296, but the results fell short of complete bilateral normality and equality in one particular: The reactions of the hindleg contralateral to the side operated on, although not maximally deficient, remained definitely depressed throughout survival periods of three and four months. In carrying out ablations of this type the greatest care was taken to avoid damaging the parts of the remnant bordering the extirpation and to leave intact the upper reaches of the internal capsule. Nevertheless the probability of producing some injury in these places was always great, and there is a likelihood that something of the kind may have been the basis for the single functional defect observed. The same result was obtained after two ablations (both on the left side) of even greater extent in which the caudal part of the posterior sigmoid gyrus was involved in the removal. Figure 6 *B*, shows the brain from one of these animals, cat 241. During a survival of six weeks this cat persistently showed in the right hindleg a submaximal deficiency of the placing reactions and a performance in hopping that approximated the decorticate condition. In striking contrast to the defect of the right hindleg was the set of perfectly normal reactions found in the right foreleg. Repeated tests failed to reveal any difference between the reactions of the two forelegs. In both they were normal and strictly comparable to the reactions of normal control animals.

When there has been a deficient hindleg and a normally acting foreleg one may invoke in explanation some disturbance which has affected the hindleg motor area situated on the posterior sigmoid gyrus without

involving the foreleg area located more rostrally on the anterior sigmoid. At least it would be reasonable to assume that such was the case in cat 241, in which it is evident that the motor area for the right hindleg must have been damaged, at least in part. Before cat 296 was killed, the cortex was explored with stimulating electrodes. From the remnant of the left cortex the usual movements of the contralateral legs were easily evoked: flexion of the right hindleg from stimulating the middle of the posterior sigmoid gyrus, abduction of the right foreleg from the outer end of the anterior sigmoid and sometimes a batting movement of this leg from the middle third of the anterior sigmoid. Throughout an hour these movements were regularly obtained from the remnant, but, though stimulation of the corresponding areas of the intact cortex gave similar movements of the left legs, the thresholds there were always very much higher and the movements less extensive. The cortex of cat 209 was not explored, but in cat 236 the two leg areas on both sides showed the same excitability and yielded movements of the same magnitude. In cat 290, which had shown some postural deficiencies of the right hindleg, stimulation revealed an even larger difference between the leg areas of the two sides than was found in cat 296. In the remnant the thresholds were lower, and the movements produced by supraliminal stimulations were greater, than in the intact cortex. In cat 241, in which the postural reactions of the forelegs were equal and normal, the movements of the forelegs induced from the anterior sigmoid gyri were equal, and the thresholds were approximately the same on the two sides. From the posterior sigmoid of the remnant, flexion of the posturally deficient right hindleg was easily obtained, but it was slight and never attained, even with strong stimulation, the massive character of the flexion induced in the posturally normal left hindleg on the application of minimal currents to the right posterior sigmoid area. Although the thresholds on the two sides appeared to be the same, stimulation of either leg area of the remnant invariably resulted in a vigorous and prolonged after-discharge involving movements of both right legs. An after-discharge did not characterize the movements obtained on stimulating the areas of the intact cortex. Without wholly discounting the results obtained on stimulating the cortices of cat 290 it is impossible to say that in these animals with remnants the integrity of the placing and hopping reactions is entirely dependent on the functional integrity of the pyramidal neurons, and that the deficiencies of the hindlegs shown by some of the animals are to be explained by some disturbance in the hindleg motor areas. Another explanation is possible and will be considered later.

At this point brief special comment should be made on the augmented excitability of the motor areas encountered in the cortical remnants of cats 290 and 296 and on the after-discharge with spreading of

effect obtained on stimulating the remnant of cat 241. It would be perhaps hazardous to draw conclusions from only three experiments. Nevertheless one cannot refrain from connecting these observations with an interesting phenomenon which was reported by Dusser de Barenne and Marshall.[7] Working on cats, dogs and monkeys, these investigators studied the effects of producing a procaine hydrochloride block of the cortex around a motor point. They were able to show that after a latency this procedure augments the excitability of the point, and that this is manifested either by a lowering of threshold or by a strengthening and spreading of the motor discharge. Furthermore, an after-discharge sometimes entered the picture. It is possible that in the three

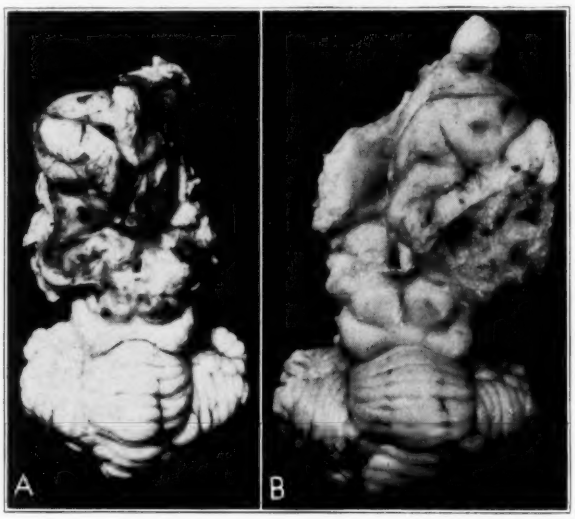

Fig. 7.—*A* is a dorsal view of the brain of cat 224. The small fragment of left cortex which remained permitted the elicitation of normal placing and hopping reactions in the right foreleg, and managed in a nearly normal way the reactions of the right hindleg. *B* shows the size and position of the remnant of the right cortex which controlled in wholly normal fashion the reactions of the left legs of cat 272.

cats mentioned a similar result was produced by surgical isolation of the motor areas of the remnant.

Proof that the Normal Functioning of a Cortical Remnant Is Not Dependent on the Cortex of the Other Hemisphere.—The absence of any evidence for an ipsilateral control of the placing and hopping reactions made it only remotely possible that the normal management

7. Dusser de Barenne, J. G., and Marshall, C.: On a Release-Phenomenon in Electrical Stimulation of the "Motor" Cerebral Cortex, Science **73**:213 (Feb. 20) 1931.

of the reactions of the contralateral legs by a remnant is in any way due to the intact cortex remaining on the other side. However, it seemed desirable to test this point by removing the cortex of the hemisphere opposite a normally functioning remnant. This was successfully accomplished in two of the three cats in which it was attempted.

The first of these was cat 224. The first operation was performed on June 11, 1931, and, as can be seen in figure 7 *A*, resulted in leaving on the left side a remnant composed of only the orbital gyrus (gyrus proreus), the sigmoid gyri and a very small portion of the lower extremity of the coronal gyrus (seen in lateral view). Immediately following recovery from the anesthetic (dial) there were moderate deficiencies in the reactions of the right legs, whereas those of the left side were normal. On the ninth postoperative day and from that time forth, the placing and hopping reactions of the forelegs were normal and equal on the two sides, and those of the left hindleg continued to show no disturbances. The only deficiency found was in the right hindleg. There the hopping reactions were as good as in the left, but the most sensitive of the placing reactions, that evoked by bringing the back of the foot against the edge of a supporting surface, was definitely defective; a development of moderate pressure against the dorsum of the foot by displacing the body forward was required before the foot was raised and put down on the edge of the table. Also this foot was invariably placed further inside the edge of the table than was the left foot. The other placing reactions of this leg appeared to be quite normal. Removal of the right cortex and a large part of the right striatum was done on Dec. 2, 1931. Thereafter, until the animal was killed seven months later, the left legs displayed the same maximal deficiencies which have characterized every animal in which the cortex of the controlling hemisphere has been removed. But the placing and hopping reactions of the right legs remained exactly as they had been in the interval between the first and second operations. These results led to the conclusion that the remnant exerted a normal control over the reactions of the contralateral foreleg and a nearly normal control over those of the opposite hindleg. They showed conclusively that the cortex of the opposite hemisphere was not essentially concerned in this control.

The initial purpose in preparing cat 272 was to remove on both sides all cortex except the frontal poles. This was attempted on the left side on March 1, 1932, and on the right on April 14, 1932. The reactions of the right legs were never normal after the operation on the left side, but the ablation on the right side did not produce the slightest permanent deficiency in the left legs. In a desire to demonstrate beyond question that a frontal remnant can, in the absence of

all other cortex, exert a normal control of these reactions the cortex remaining on the left side was removed in a third intracranial operation, performed on July 23, 1932. In accord with expectations it was found that in the first operation the ablation had extended into the posterior sigmoid from behind and had also involved the borders of the cruciate sulcus at its lateral extremity. There can be no doubt that the motor areas of both right legs had been impaired by lesion and partial extirpation. From July 23 until it was killed on Nov. 7, 1932, this cat lived with its brain in the condition shown in figure 7 *B*. The cortex

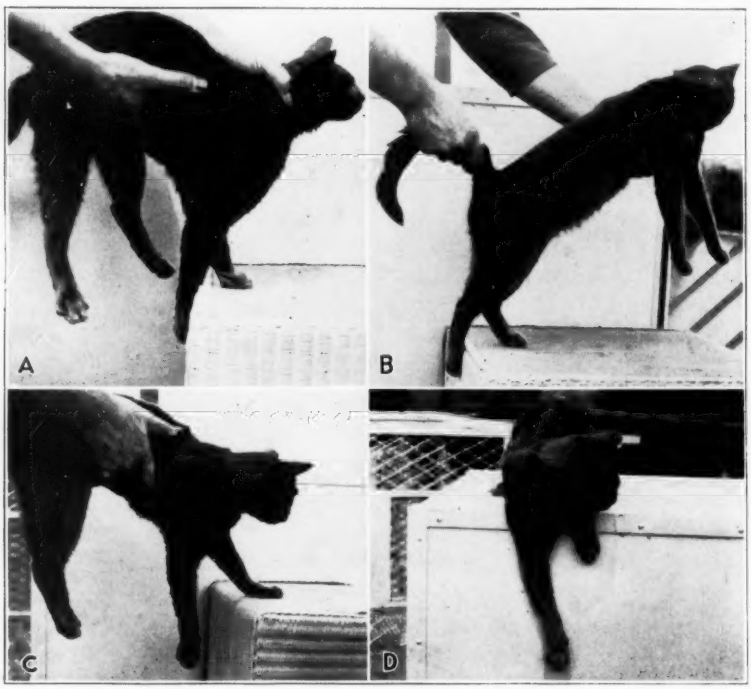

Fig. 8.—Photographs of cat 272 taken three weeks after the third intracranial operation (fig. 7 *B*). The presence of normal placing reactions in the left legs (under the control of the remnant of right cortex) and their failure in the right legs (opposite the decorticated left hemisphere) are clearly indicated.

composing the remnant was of somewhat greater extent than that in cat 224. In addition to the frontal and both sigmoid gyri there remained the rostral part of the longitudinal gyrus and a narrow strip consisting of the cranial portions of the coronal and suprasylvian gyri. Except for a few days following the second and third operations, the placing and hopping reactions of the left legs were wholly normal (fig. 8). It may be mentioned that enucleation of the eyes three days before killing this

cat left these reactions unmodified, a result which could have been reasonably predicted.

Before cats *224* and *272* were killed, they were anesthetized with dial and the remaining fragment of cortex was explored faradically with bipolar electrodes. In cat *224* the anesthesia was unfortunately very deep, and the results of electrical stimulation were limited. With strong currents it was possible to obtain from the lateral half of the anterior sigmoid gyrus and from no other cortical area a slow but definite abduction of the right foreleg. Late in the experiment, stimulation at this point also caused the tail to move forward between the hindlegs. From the part of the posterior sigmoid gyrus which forms the caudal edge of the remnant a slight flexion of the right hindleg was obtained with strong currents. When the electrodes were applied to the dorsal surface of the exposed left caudate nucleus, much weaker currents evoked maximal flexion of the right hindleg together with vigorous batting movements of the right foreleg. These movements were doubtless due to stimulation of corticofugal fibers in the internal capsule. The testing of the electrical excitability of the remnant on the right side in cat *272* was favored by a light dial anesthesia; it yielded brisk movements in the musculature of the left side. This remnant was explored repeatedly, and the following movements were uniformly evoked with very weak currents barely perceptible on one's tongue: from the outer half of the anterior sigmoid gyrus, abduction of the left foreleg at the shoulder and sometimes a backward pawing movement of this leg; from the tissue bordering the medial arm of the ansate sulcus, strong flexion in all joints of the left hindleg, and from the lower rostral portion of the coronal gyrus, movements of the vibrissae of the left side. Both in this cat and in cat *224* no ipsilateral movements were obtained from the remnant.

The results obtained with these animals settle in a positive manner the question of the capacity of a small frontal remnant to manage in normal fashion the placing and hopping reactions of the contralateral legs. This it can do as perfectly as when it is in full anatomic and physiologic connection with all other parts of the cortex. In spite of overwhelming evidence that cortical control of the reactions is entirely contralateral, the objection may be raised that since in the brains of cats *224* and *272* the remnant was for a period acting in the presence of contralateral cortex the latter may have contributed to its ability to maintain a normal function. But the results with cat *272* indicate that such an interpretation is well-nigh inadmissible. In a second operation the remnant on the right side, which managed the contralateral reactions normally, was left after a functionally very deficient remnant had been left on the other side.

The normal control of the placing and hopping reactions is not the only function carried out by these single small cortical remnants. That they contribute a number of elements to the behavior of their possessors is demonstrated by the various ways in which cats 224 and 272 differed from the decorticate animals. They moved about much more, and all who observed them agreed that their locomotion was normal, whereas the gait of a wholly decorticate cat is slightly but definitely abnormal, and the body tends to be carried in a somewhat crouching posture with head held low. Furthermore, these cats with a frontal fragment seldom showed any trace of the peculiar attitudes of the legs that characterized the decorticate animals. They kept themselves clean, and spent much time in licking their coats, on the side of the remnant as well as on the opposite side. Attention may also be called to the fact that cats 224 and 272 were able to find and eat their food and to compete for it successfully with the normal cats which shared their room in the animal quarters. Although a cat without neocortex may eat of its own accord and even find its food within small spaces, it is incapable of this sort of behavior. There were other important differences between the two types of preparation, but enough has been said to show that a frontal remnant confers on a cat many capacities which are lacking after decortication. This is a matter which deserves further investigation, and work in this direction is being carried on.

Relation of the Motor and Sensory Leg Areas and of the Area Frontalis to the Placing and Hopping Reactions.—From the experience gained in the study of cortical remnants it may be concluded that the cortical mechanism which controls these postural reactions has its location within an area which comprises the gyrus proreus (frontal or orbital gyrus), the anterior and posterior sigmoid gyri, the upper part of the coronal gyrus and the rostral portion of the longitudinal gyrus. Provided this area is left intact and regardless of whether any other cortical tissue of either hemisphere remains, the reactions of the contralateral legs are normal. It is known that the following functional divisions are located within this region: the greater part of the electrically excitable areas, including the foreleg and hindleg motor areas; a very large part of the cortical representation of cutaneous and deep sensibility of legs and head, and the area frontalis. Do the reactions depend on any one of these cortical elements, or are they an expression of a functional combination of two or all three of them?

The position of the area frontalis or intermediate motor area in the cat has been determined by Langworthy.[8] As in other mammalian

8. Langworthy, O. R.: The Area Frontalis of the Cerebral Cortex of the Cat, Its Minute Structure and Physiological Evidence of Its Control of the Postural Reflex, Bull. Johns Hopkins Hosp. **42**:20, 1928.

brains, it lies just rostral to the electrically responsive cortex, and in this particular case extends from the edge of the cruciate sulcus forward and downward over the upper part of the gyrus proreus, which forms the rostral extremity of the frontal pole. It also extends for some distance on the medial surface of the hemisphere. Laterally the gyrus proreus is clearly delimited by the orbital (presylvian) sulcus, but caudally it fuses with the anterior sigmoid, and in this region the type of cortex gradually changes to that typical of the electrically excitable areas. According to Olmsted and Logan,[9] King [10] and Langworthy,[8] ablation of the area frontalis produces in the cat an abnormal and enduring hypertonia of the contralateral legs which is not found after extirpation of the electrically responsive leg areas. In view of this reported relationship of the area frontalis to a postural function, it was

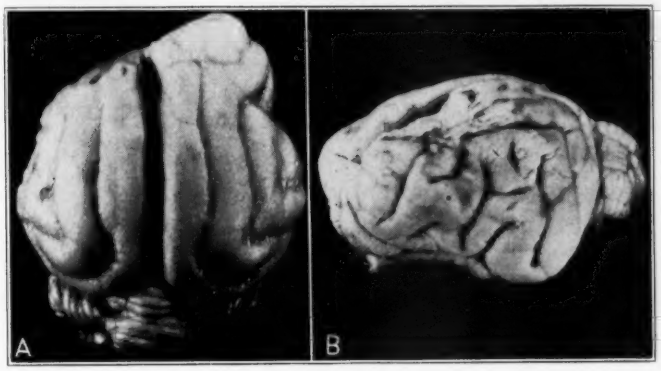

Fig. 9.—The brain of cat 225, which exhibited normal placing and hopping reactions in the left legs, is shown in *A*. The left hemisphere of cat 240 is seen in *B*. The hindleg sensory area had been largely removed, but the motor areas for the right legs and the foreleg sensory area remained intact.

obviously a matter of interest and importance to determine whether this region has any part in the management of the placing and hopping reactions. The investigators just mentioned employed a direct approach to this part of the cortex through the frontal sinus, but, as has already reported relationship of the area frontalis to a postural function, it was found more satisfactory to extirpate the area frontalis through the usual temporoparietal defect in the skull after the other frontal pole had been removed. The incidental ablation of tissue from the other hemisphere is made justifiable by the fact that the cortical control is wholly crossed.

9. Olmsted, J. M. D., and Logan, H. P.: Cerebral Lesion and Extensor Rigidity in Cats, Am. J. Physiol. **72**:570, 1925.

10. King, W. T.: Observations on the Rôle of the Cerebral Cortex in the Control of the Postural Reflex, Am. J. Physiol. **80**:311, 1927.

In all five animals submitted to this operation the reactions of the legs opposite the ablated area frontalis remained normal. The brain of one of these animals, cat 225, is shown in figure 9 *A*. The medial two thirds of the right anterior sigmoid gyrus as well as the entire gyrus proreus had been removed, and therefore there had been some loss of tissue from which movements of the left foreleg could usually be obtained on stimulation. This leg, however, showed no deficiencies, and two months after operation it was found that the usual movements could be induced in it by minimal currents applied to the remaining lateral portion of the anterior sigmoid gyrus. In the four other animals of this group the ablation was similarly done, but was limited to the gyrus proreus and the medial fourth of the anterior sigmoid (thus removing Langworthy's areas A, G, H and I). These results demonstrate that the area frontalis is not an essential part of the cortical mechanism which controls the placing and hopping reactions. Although the matter of decorticate extensor rigidity will be considered in a separate report, it may be said here that it has so far been impossible to confirm the assertion that removal of the area frontalis produces any sort of extensor hypertonia. On the other hand, whenever the sigmoid gyri have been included in an ablation, some degree of contralateral extensor rigidity has invariably ensued.

On the basis of personal experience, the electrically excitable leg area in the cortex of the cat may be said to be located only in the parts bordering the cruciate sulcus. Responses of the contralateral foreleg have resulted only from stimulation at the lateral extremity of the sulcus and over the lateral two thirds of the anterior sigmoid gyrus. Contractions of the musculature of the opposite hindleg have been obtained from varying points on the posterior sigmoid gyrus. In general, these results are in harmony with the observations of other investigators (e. g., King [10] and Langworthy [8]), but Stout,[11] who has made a most extensive study of these regions in the cat, included the posterior sigmoid in the foreleg motor area. He found, however, that the hindleg area did not extend behind the ansate sulcus, and he stated that the coronal sulcus marks the lateral border of the excitable region. Reference to previous statements will recall that these regions have been involved in every ablation which was followed by permanent maximal deficiencies of the contralateral placing and hopping reactions. Furthermore, it is evident that they have invariably been included in cortical remnants which conferred normal reactions on the contralateral legs. In several such instances their excitability has been determined. These facts suggest that the motor areas for the legs represent the cortical

11. Stout, J. D.: On the Motor Functions of the Cerebral Cortex of the Cat, Psychobiol. **1**:177, 1917.

mechanism for the postural reactions. This possibility is not favored, however, by the results obtained in cat 290. It will be remembered that this animal had persistently shown for more than ten weeks a nearly maximal deficiency of the reactions in the hindleg opposite the remnant. But on comparing the excitability of the hindleg area of the intact hemisphere with that of the remnant it was found that the latter had a lower threshold and gave movements of greater magnitude than did the former. A similar result was obtained in cat 241.

The nature of the reactions makes it certain that the cortical representation of the sensibility of the legs must be taken into consideration. The only satisfactory knowledge on this subject, so far as the cat is concerned, has come from the studies of Dusser de Barenne.[12] As all who have studied the effects of cortical ablations must realize, the sensory defects which are produced by even extensive extirpations are extremely difficult to appraise. This obstacle to the study of cerebral sensory functions in animals was overcome by the method of local strychninization which Dusser de Barenne has employed to such great advantage. It gives, instead of a sensory defect, symptoms of sensory excitation, and the animal shows spontaneously to what part of the body sensory disturbances are referred. Furthermore, the evidence is convincing that the action of strychnine, when it is properly applied, is strictly localized. This method has shown that in the cat's cortex the sensory areas for the foreleg and hindleg lie quite separately within the zone which represents the cutaneous and deep sensibility of the body. The foreleg area comprises the anterior sigmoid gyrus, the part of the posterior sigmoid gyrus lying rostral to the small postcrucial sulcus (Campbell's "compensatory ansate fissure"), the frontal half of the anterior suprasylvian gyrus and the middle third of the anterior ectosylvian gyrus. The focal part of this zone is in the sigmoid region. The hindleg sensory zone occupies the rostral half of the longitudinal gyrus, and its focal area lies in its rostral part. The head area, which may be of importance in two of the placing reactions of the forelegs, almost entirely overlaps the foreleg area. It is evident that the sensory and motor foreleg areas overlap, but that the former is the more extensive. On the other hand, the sensory and motor hindleg areas occupy separate places on the convexity of the hemisphere. Furthermore, the experiments of Dusser de Barenne show that in the case of cutaneous sensibility both sides of the body are represented in the cortex of each hemisphere, but that the contralateral representation is more pronounced than the ipsilateral. Deep sensibility, however, has only a contralateral representation.

12. Dusser de Barenne, J. G.: Experimental Researches on Sensory Localizations in the Cerebral Cortex, Quart. J. Exper. Physiol. **9**:355, 1916.

Turning to the application of these facts to the analysis of the cortical control of the placing and hopping reactions, it is certain that the separate surgical removal of the sensory and motor areas for the foreleg is impossible. But this can be done in the case of the hindleg areas, and has been attempted in four cats. In each the ablation was restricted to the rostral half of the longitudinal gyrus (the hindleg sensory area) and a part of the adjacent suprasylvian gyrus which was incidentally removed. In only one of these, cat 240, the brain of which is shown in figure 9 *B*, was the entire focal portion of the hindleg area removed. The lesion was on the left side. During its postoperative survival of five weeks the cat showed normal reactions in both forelegs and in the left hindleg, but there were certain constant disturbances in the right hindleg: a nearly maximal deficiency of the hopping reactions and of that placing reaction which occurs when the dorsum of the foot is brought in contact with the edge of a supporting object. The other placing reactions of this leg seemed within the normal range. Tests of the leg motor areas showed equal thresholds and the same magnitude of response on the two sides. Similar but less pronounced defects of the contralateral hindleg were found in the three other animals, but in each a little of the focal part of the hindleg zone had been spared. In all four the sensitivity of the foot of the affected hindleg to pinching was less than that of the foot of the opposite side.

A better criterion of the rôle played by the sensory cortex is found in a consideration of the results obtained when frontal remnants were left. In every case in which Dusser de Barenne's hindleg area was not included in the remnant there were definite if not maximal deficiencies in the reactions of the opposite hindleg (cats 224, 231 and 241). On the other hand, the rostral focal portion of the area was present in every fragment which exerted a normal control over the contralateral hindleg (cats 209, 236, 272, 296 and 352). The foreleg sensory area was left largely intact together with the motor area in every cat which possessed normal reactions in the opposite foreleg.

The hypothesis which seems best to fit the experimental facts is that the sensorimotor zone contains the neural mechanism which subserves these postural reactions. Since many ablations of the frontal pole which produced maximal contralateral deficiencies left the hindleg sensory area apparently intact, but removed the motor area, it is probable that the sensory cortex acts through the motor mechanism. Just why in some cases the defects following removal of the hindleg sensory area fell somewhat short of being maximal (cats 224, 240 and others) is not clear. A little of the sensory cortex may have been left. This contingency makes it impossible to say that sensory decortication does not produce as great an effect as motor decortication. On the whole, it

must be said that the paucity of relevant experimental facts and the great difficulty of operating selectively in such a small cortical area prevents, for the present at least, the drawing of definite conclusions concerning the intimate functional relationship of the motor and sensory areas.

COMMENT

A survey of the literature on the subject of cortical localization clearly reveals that the term "localization" has been used with a flexibility of meaning that is, to say the least, confusing. It is perfectly true that localization is a relative matter, but it is unfortunate that the precise connotation attached to the word itself has been so seldom declared. To apply a rigorous definition, it may be said that a cortical function is localized only when a small area contains all the cortical tissue essentially concerned in the cortical control of that function. The experiments which have been described show that the cortical management of the placing and hopping reactions has the degree of localization demanded by this strict definition. Permanent deficiencies have invariably followed removal of a small area at the rostral pole of the hemisphere. Since no greater defects were produced by removal of the hemisphere they may be regarded as representing a maximal cortical deficiency. But this evidence alone does not satisfy the requirements of the definition. It leaves unexplored the possibility that other parts of the cortex normally make essential contributions to the function of the part the removal of which has invariably produced a maximal defect. Therefore a true measure of the localization was obtained only when it was determined how much cortex could be removed without disturbing the placing and hopping reactions. The observations on cats which retained of the entire cortex only a small rostrally situated remnant demonstrate conclusively that this particular cerebral control is actually restricted to a rather small fraction of the neopallium.

The minimal area the removal of which produces a maximal deficiency does not coincide exactly with the area represented by any one of the normally functioning remnants. The former is smaller than the latter, but lies within it. The most satisfactory interpretation of this fact, namely, that the essential cortical mechanism comprises both motor and sensory elements and that the sensory cortex acts through the motor, has already been sufficiently discussed. Before the view that the deficiencies were due to a sensorimotor disturbance can be adopted with any assurance, it will be necessary to rule out another possible interpretation which the experimental facts suggest. In every case in which the sigmoid gyri have been removed, whether in an ablation of the frontal pole or in a complete unilateral decortication, some degree of extensor rigidity resulted in the contralateral legs. This rigidity was bilateral after bilateral removals of these two types. It cannot usually be detected

during standing, but when the animal is suspended, the rigidity manifests itself by an extensor position of the leg and an abnormal resistance to passive flexion. It varies considerably from animal to animal, but is always more pronounced in the hindlegs than in the forelegs. In fact, it is an almost invariable accompaniment of deficient placing and hopping reactions. This raises the question whether their failures and defects are not due to a fixation of the leg by the rigidity. On the whole, it seems that a distinctly negative answer can be given. In the large series of experiments considerable differences in the intensity of the rigidity were found, but were not correlated with any variations in the degree of deficiency of the postural reactions. When the rigidity was great in the hindlegs and slight in the forelegs, the reactions were as defective in the latter as in the former. During considerable parts of their periods of survival, three of the unilaterally hypothalamic cats showed no trace of this rigidity in the contralateral legs, yet the placing and hopping reactions of these legs remained maximally deficient. In the four cats in which removal of the hindleg sensory area produced some deficiency of the placing and hopping reactions of the opposite hindleg, this extremity showed no rigidity. Furthermore, as Brooks [13] has found, in the rat certain cortical ablations produce similar deficiencies of the same placing and hopping reactions as have been studied in the cat. But neither these nor any other cortical removals induce rigidity in this animal. In view of these facts it seems safe to assert that the rigidity per se does not produce the deficiencies.

This investigation had its origin in an attempt to analyze the attitudinal peculiarities shown by decorticate cats and cats without neocortex. When, as a result of Rademaker's work, it was realized that these animals lack placing reactions and possess only vestiges of the hopping reactions, it was thought that a full explanation was at hand. But as the study of localization progressed certain observations threw some doubt on the adequacy of that interpretation, and it must be admitted that the matter is not yet wholly clear. For example, the cats without frontal poles were as deficient in respect to the placing and hopping reactions as the decorticate animals, but their legs rarely assumed such abnormal positions. Similarly, after unilateral decortication or removal of one frontal pole the contralateral legs were only occasionally seen in abnormal attitudes although they were maximally deficient as regards the placing and hopping reactions. One of the animals without frontal poles (cat 298) was blinded by enucleation of the eyes some time before being killed. Following this operation the animal showed the same striking tendency to assume abnormal attitudes

13. Brooks, C. M.: Studies on the Cerebral Cortex: II. Localized Representation of Placing and Hopping Reactions in the Rat, Am. J. Physiol., to be published.

as did the decorticate animals. The impression thus given was that vision, which was certainly not appreciably disturbed by removal of the frontal poles, had somehow prevented the attitudinal abnormalities. In an investigation soon to be reported, Orias and I have shown that extirpation of the frontal poles (including the foreleg sensorimotor cortex) does not abolish the visual placing reaction of the forelegs, but that removals that just include the area striata deprive the animal of this response. These facts suggest that placing of the feet in response to visual stimuli is the factor which permits the degree of attitudinal normality shown by animals in which the nonvisual placing reactions and the hopping reactions are maximally defective. But that this is not the whole story is indicated by the fact that cats 224 and 272, which lacked all cortex except one frontal pole, showed only slight tendencies to stand or sit with the legs in abnormal positions. Furthermore, as Brooks [13] showed, rats do not possess any trace of the visual placing reaction, and when wholly decorticate they do not show the peculiar attitudes of the legs that characterize the decorticate cats, although they are practically as deficient in the nonvisual placing and the hopping reactions as the cats.

The fact has long been recognized that decorticate dogs and cats are able to walk and run in a fairly normal fashion. The well known investigations of Sherrington and of Magnus have brought to light a large number of important postural reflexes the central control of which is definitely subcortical. These data have naturally created the impression that quadripedal locomotion and posture depend on the brain stem, cerebellum and spinal cord. Therefore it may occasion some surprise that one set of postural adjustments, the placing reactions, is entirely dependent on the cerebral cortex, and that this highest part of the brain has an important rôle in the normal management of another group, the hopping reactions. But Rademaker,[3e] who discovered these items of behavior, showed that the capacity normally to attain and maintain a standing posture depends on a large number of reactions the control of which varies in level from the spinal to the cortical. It is in accord with the general conception of cortical functions that these cortically managed reactions have to do with the finer adjustments of postures which are developed by subcortical levels of integration. Rademaker regarded the placing reactions which he has described in the dog as conditioned reflexes, and it has been possible to confirm in the cat the evidence with which he supported this view. The reactions are not present in young animals, and in certain instances it is possible to subject them to a process of "experimental extinction." [14] Although I am inclined to concur in Rademaker's opinion, it would perhaps be

14. Rademaker,[3e] pp. 26 and 35.

well to obtain further experimental evidence before coming to a final decision on this point.

It is interesting to compare the results of the present work with the observations of Lashley. From his extensive studies on cerebral function in learning, Lashley accumulated a body of evidence which led him to state that "in various cortical functions there is every degree of specialization from a limited point to point correspondence of cells to a condition of absolute non-specificity."[15] Nonspecificity is perhaps best illustrated by the effect of cortical lesions on the amount of practice necessary for rats to learn a complex maze (Lashley[16]). A slowing of the process appeared no matter where the cortical lesion was made, but showed a high correlation with the percentage of neocortex destroyed. Equal amounts of destruction in various areas (motor, somesthetic, auditory and visual) provided equal amounts of retardation, and the evidence indicated that the normal contribution of any given area is nonspecific; e. g., the visual cortex exerts an influence which is not visual, for blinding does not interfere with the learning, whereas destruction of visual cortex in blinded rats does produce a retardation. A somewhat similar phenomenon was discovered in testing the influence of visual cortex on the retention of an acquired reaction to brightness. It was found (Lashley[17]) that this part acts as a unit to produce a "mass facilitation" of a function which subcortical nuclei can carry out in the absence of visual cortex. In this case there is a certain degree of localization, for the visual area and no other part of the cortex exerts this effect. But within the area, which forms about one third of the neocortex, there seems to be no specialization of parts in the performance of the function. When pattern vision was studied, the degree of localization was found to be much greater. From a statistical analysis of his results Lashley[18] concluded that bilateral destruction of a small specific region situated laterally in the area striata abolishes in rats the capacity to distinguish patterns as effectively as destruction of the entire occipital cortex. Lesions in the medial portions of the striate area and extensive destructions in the motor and somesthetic areas had no effect on this visual function. The instance of a spatially restricted cortical function which has been demonstrated in the present report

15. Lashley, K. S.: Mass Action in Cerebral Function, Science **73**:245 (March 6) 1931.

16. Lashley, K. S.: Brain Mechanisms and Intelligence, Chicago, University of Chicago Press, 1929.

17. Lashley, K. S.: Studies of Cerebral Function in Learning: VII. The Relation Between Cerebral Mass, Learning and Retention, J. Comp. Neurol. **41**:1 (Aug. 15) 1926.

18. Lashley, K. S.: The Mechanism of Vision: IV. The Cerebral Areas Necessary for Pattern Vision in the Rat, J. Comp. Neurol. **53**:419 (Dec. 15) 1931.

seems to bear a resemblance to the last of the three examples taken from the studies of Lashley. The experiments give no indication of any "mass action" on the part of the area which controls the placing and hopping reactions. Instead, there is evidence that functionally distinct portions of the area make their specific contributions. A comparison of the two cases in respect to the extents of the essential cortical areas is impossible, for Lashley has not determined just how small an area can be left without disturbing pattern vision. In an early paper Lashley [19] concluded that the motor cortical areas and the caudate nuclei are together concerned with the general regulation of posture, but that neither is directly involved in the performance of learned activities. If the placing reactions are learned responses this conclusion is too general, but the suggestion that the motor cortex is concerned in postural functions is in accord with the specific results of the present work. The evidence, however, distinctly shows that the caudate nuclei have nothing to do with the postural reactions under consideration.

The present state of knowledge of cortical functions is so meager that any attempt to evaluate one set of observations in terms of another or to correlate data of diverse origins is apt to lead to error and confusion. Particular restraint is necessary in discussing the subject of localization of function. It is important to recognize the probability that while some functions are widely represented in the cortex, others are narrowly restricted. Much of the writing on this subject has shown an unfortunate tendency vigorously to affirm one of these extremes and categorically to deny the other. In the present case one need only insist that the cortical management of two sets of rather simple postural reactions is strictly localized and to point out that cortical remnants are capable of normal function.

SUMMARY

Chronic experiments on cats have shown that in this species two sets of postural adjustments, the hopping reactions and the five placing reactions which occur in response to cutaneous and proprioceptive stimuli, have a strictly localized cortical control. The localization was determined by the following experimental facts:

1. Removal of the gyrus proreus and sigmoid gyri and incidental ablation of a small part of either the coronal or the longitudinal gyrus resulted in permanent disturbances of the reactions of the contralateral legs. The deficiencies consisted in a complete failure of the five placing reactions and a profound depression of the hopping reactions. This condition represents a maximal cortical deficiency, for complete unilateral decortication or removal of all tissue of one hemisphere above

19. Lashley, K. S.: Studies on Cerebral Function in Learning: III. The Motor Areas, Brain **44**:225, 1921.

the hypothalamus produced no greater disturbances in the reactions. The absence of ipsilateral effects showed that the control is entirely contralateral.

2. Bilateral removal of the same frontal area was followed by a permanent maximal deficiency of the reactions of all four legs. Cats so operated on were as defective in respect to these reactions as animals lacking all neocortex or as wholly decorticate preparations.

3. Bilaterally equal deficiencies were produced when the entire cortex and striatum of one hemisphere and only the sigmoid gyri and gyrus proreus of the other side were ablated.

4. The reactions of the contralateral legs were not modified by removal of temporal or occipital cortex or of the gyrus proreus.

5. The reactions remained normal in both contralateral legs after extirpation of all cortex except the sigmoid gyri, the gyrus proreus, the rostral part of the longitudinal gyrus and a small fraction of the coronal gyrus. This result was not modified by total ablation of the opposite cortex.

Stress is laid on the fact that a remnant of rostral cortex is able to manage in normal fashion the placing and hopping reactions of the opposite legs. This shows conclusively that the representation of these reactions is strictly localized and functionally independent of all other cortical areas.

Evidence is presented which suggests that the essential cerebral mechanism consists of sensorimotor cortex. There is some indication that the sensory cortex exerts its influence through the motor (pyramidal) projection area. The area frontalis is not involved in the control.

The tendency of decorticate cats to assume peculiar attitudes of the legs is largely, but probably not entirely, attributable to the deficiencies of the placing and hopping reactions.

XANTHOMATOSIS AND THE CENTRAL NERVOUS SYSTEM

(SCHÜLLER-CHRISTIAN SYNDROME)

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Xanthomatosis, the Schüller-Christian syndrome, generally characterized clinically by the symptom triad of defects in the membranous bones, exophthalmos and diabetes insipidus, has been recognized as a systemic disease. Histopathologically, the disease is characterized by a diffuse collection of lipoid cells ("foam cells"), cellular reactions and fibrosis in various organs of the body. The granulomatous collections within the skull and dura mater giving rise to neurologic symptoms have been described frequently. The polyuria and polydipsia are believed to result from pressure on the hypophysis and tuber cinereum or from direct invasion of these structures by such lipoid masses. Although the lesions of the pituitary gland and tuber cinereum have been reported by a few observers, involvement of the rest of the neural structures, as far as could be ascertained, has not been recorded before. The neurologic and neuropathologic findings in this case were of sufficient importance to warrant a separate report.

For a careful review of the literature on the general aspect of this symptom triad, first described by Hand [1] and later by Schüller [2] and Christian,[3] the reader is referred to the contributions of Chiari [4] and others.

Read at a meeting of the American Neuropathology Club, Dec. 28, 1931.

From the Neuropathological Laboratory and Neurologic Division, Montefiore Hospital.

1. Hand, A.: Polyuria and Tuberculosis, Arch. Pediat. **10**:673, 1893. Kay, T. W.: Acquired Hydrocephalus with Atrophic Bone Changes, Exophthalmos and Polyuria, Pennsylvania M. J. **9**:520, 1905.

2. (*a*) Schüller, A.: Ueber eigenartige Schädeldefekte im Jugendalter, Fortschr. a. d. Geb. d. Röntgenstrahlen **23**:12, 1916; (*b*) Dyostosis Hypophysaria, Brit. J. Radiol. **31**:156 (April) 1926.

3. Christian, H. A.: Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus, Contributions to Medical and Biological Research, New York, Paul B. Hoeber, Inc., 1919, vol. 1, p. 390.

4. Chiari, H.: Die generalisierte Xanthomatose vom Typus Schüller-Christian, Ergebn. d. allg. Path. u. path. Anat. **24**:396, 1931.

REPORT OF A CASE

Clinical History.—P. S., a man, aged 27, born in New York of Russian-Jewish parents, a teamster, was admitted to the Montefiore Hospital on May 9, 1928, complaining of discharge from the left ear, fistula in ano, sinus of the right thigh, frequency of urination and marked thirst. In the summer of 1923, at the age of 22, the patient experienced pain in one of the right upper molars. The tooth was extracted, and at the site of extraction some granulation tissue appeared. Most of his teeth became loose and fell out. In June, 1925, part of the lower jaw was resected for a so-called multilocular cyst. Pathologic examination of this tissue led to a diagnosis of granuloma or neoplasm of the reticulo-endothelial system. Three months later the granuloma recurred. At the end of 1926, the patient complained of polyuria and polydipsia. In 1927, chronic eustachian salpingitis, fissure in ano, pain and bursitis of the left hip and pain in the left axilla and in the right femur developed. On histopathologic examination, material from these regions was shown to consist of granulomas and granulation tissue. In December, 1927, the patient voided as much as 11 liters of urine a day; this quantity was reduced to 3.5 liters a day by the administration of pituitary. Roentgen examination at this time disclosed a normal sella turcica, rarefaction in the occipital bones and destruction of the trochanter of the right femur.

Except that the father had asthma and eczema, the family history was without significance. The patient had scarlet fever when 8 years old, was injured in an elevator shaft and fractured his nose and skull at 13 and had rheumatism of the knees and ankles lasting for two months at 21. He said that he had not had a venereal infection.

Physical Examination.—On admission, in 1928, the patient weighed 205 pounds (93 Kg.). There were: female distribution of the pubic hair, purulent discharge from both ears, a mastoid scar behind the left ear, only two teeth in the upper jaw, absent mandible, a thickened nose from an old injury, a draining sinus in the left axilla and the left thigh and a fistula in ano. Neurologic examination at this time gave negative results.

Laboratory Data.—Roentgen examination disclosed destruction of the inner and outer tables of the parietal bones (fig. 1), of the clinoid processes of the sella turcica, of the shaft of the right femur and of the right wing of the sacrum. The fluid intake was from 2,700 to 3,800 cc. a day, and the urinary output from 2,300 to 2,700 cc. as long as the patient received pituitary. Examination of the blood gave essentially normal results. Chemical examination of the blood showed: urea nitrogen, 6.4 mg., and sugar, 0.14 mg. per hundred cubic centimeters. The blood pressure was 100 systolic and 66 diastolic. Material taken for biopsy from the axilla and anus showed granuloma.

Course.—The patient received pituitary, 1 ampule a day, and deep roentgen therapy for the discharging sinuses and the defects in the bones of the skull. The polyuria was checked as long as the patient received pituitary. The discharge from the ears and sinuses became less profuse.

On Sept. 11, 1929, neurologic examination revealed: horizontal nystagmoid twitches in both directions; peripheral paralysis of the left side of the face and loss of taste over the left anterior two thirds of the tongue. The roentgenologic findings were the same as at the previous examination. The bones of the skull showed a moderate amount of bone production in the diseased area. The patient was discharged in January, 1930.

From the time of discharge to the time of readmission (January, 1931) the patient received deep roentgen therapy twice a week in the outpatient department. His condition remained stationary for about eight months, when severe frontal headaches, tremor of both hands, weakness of the lower extremities, unsteady gait and blurred vision suddenly developed. Roentgen examination of the nasal accessory sinuses disclosed a cloudiness of the left antrum.

Second Admission.—Physical Examination: Except for an enlarged liver and larger hands and feet than are normally found, the examination gave the same results as on the first admission.

Neurologic Examination: There were dragging of the right lower extremity ("osteomyelitis" of the femur), diminished power in all extremities, more so on the right, generalized hyperreflexia, bilateral ataxia, suggestive Gordon-Holmes sign on the right, dysdiadokokinesis bilaterally, coarse tremor of the outstretched hands, slight intention tremor of the hands, normal sensation throughout, left palpebral fissure, with the left pupil smaller than the right, nystagmoid jerks on extreme gaze to the right, questionable pallor of the right optic nerve head, hypalgesia, thermohypesthesia and hypesthesia over the distribution of the left fifth nerve, impaired taste over the left anterior two thirds of the tongue, peripheral paralysis of the left side of the face, slight involvement of the left eighth nerve, and polyuria and polydipsia. Libido and potency were unimpaired.

Laboratory Data: On Jan. 13, 1931, the urine was normal, except for a low specific gravity. The Wassermann test of the blood gave negative results. The blood serum contained: cholesterol, 152 mg. per hundred cubic centimeters (normal, from 150 to 190); urea nitrogen, 7.7; total fat, 1.71 per cent (normal, 0.7 per cent); albumin, 4.71 per cent; globulin, 3.23 per cent; calcium, 9.8 mg.; phosphorus, 3.9 mg. A sugar tolerance test showed: fasting, 89 mg.; one hour after a meal, 110 mg.; two hours, 86 mg. The basal metabolic rate was: (1) +1 per cent; (2) —4 per cent. The blood pressure was 110 systolic and 80 diastolic. Examination of the blood disclosed a moderate secondary anemia, with considerable central achromia. The icteric index and van den Bergh tests were negative. The congo red test gave negative results. The sedimentation time was forty-four minutes. An electrocardiogram showed bradycardia and occasional ventricular extrasystoles. Roentgen examination revealed the same changes as those recorded during previous examinations.

Further Course.—The patient became progressively weaker and died of a pulmonary infection on March 4, 1931.

NECROPSY

General Body Tissues: On gross examination the calvarium of the skull showed a punched-out area of rarefaction in the parietal region (fig. 1). A large portion of the cortex of the bone in this region was eroded. Several irregular thickenings of the calvarium were found in the area of erosion. Grayish-yellow, stellate-shaped nodules were found in the lungs.

Microscopic examination revealed typical "foam cells" in the bones of the skull, right femur, mandible, maxilla, lungs and the pituitary gland.

Pituitary Gland: In the loose areolar connective tissue outside the pituitary gland was a collection of "foam cells" (fig. 2), with an occasional lymphocyte. The anterior portion of the pituitary gland showed a striking decrease of oxyphilic cells. The region of the pars intermedia of the posterior portion of the pituitary gland was invaded by groups and islets of acidophilic and basophilic cells.

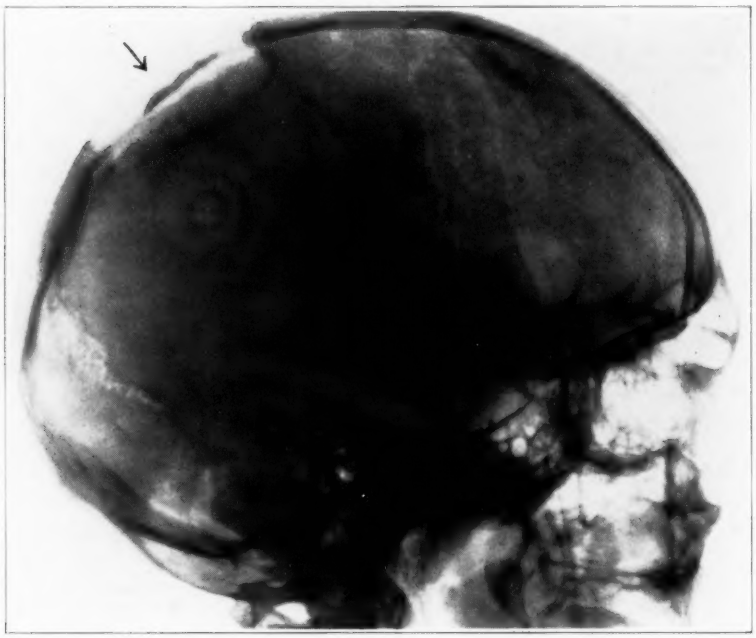

Fig. 1.—Lateral view of the skull, showing destruction of the inner and outer tables of the parietal bones.

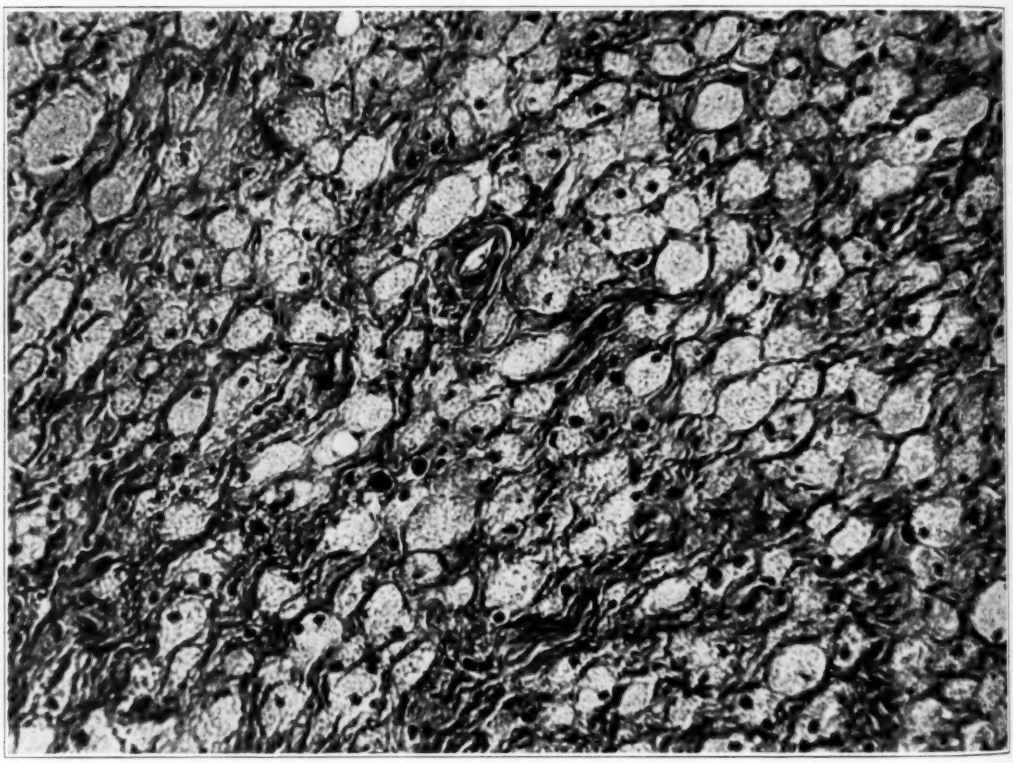

Fig. 2.—"Foam cells" found in the loose areolar connective tissue outside the pituitary gland. Hematoxylin-eosin stain; × 100.

Central Nervous System.[5]—Gross examination of the brain revealed that the cerebral vessels were congested; the convolutions, normal. The brain was cut coronally. Except for a slightly spongy appearance of the white matter of the parietal region, no gross abnormality was discovered.

Microscopic Examination.—Celloidin sections from the various convolutions and sections through the basal ganglia, tuber cinereum, pons, cerebellum and medulla oblongata were stained by the myelin sheath (Weil modification), hematoxylin-eosin, van Gieson, cresyl violet and Holzer methods. Frozen sections from various regions were stained by the sudan IV, Cajal gold sublimate (Globus modification), Schultze-Stoehr, silver carbonate (Penfield modification) and Victoria blue methods. The region of the tuber cinereum, embedded in celloidin, was cut serially, and every tenth section was stained by the modified Bielschowsky method (Kernohan modification) in addition to the methods already mentioned.

The white matter of most of the cerebral convolutions, and that of the superior parietal region especially, showed scattered plaques of demyelinization (fig. 3*A*). The myelin in these plaques had completely disappeared and was replaced by irregularly shaped, swollen cells. At the periphery of the demyelinated areas there was fragmentation of the myelin sheaths. In the cresyl violet sections the demyelinated plaques were stained more densely than the rest of the white matter (fig. 3*B*). A higher power lens showed that the deeply stained areas consisted of groups of large cells, irregularly shaped, with pale cytoplasm and irregularly and darkly stained nuclei, generally situated at the periphery of the cell (fig. 4*A* and *B*). Occasional multinucleated cells and mitosis were seen. Some of the cells contained vacuoles. Between the large cells there were numerous glia cells of the oligodendroglia and astrocytic varieties. The large, irregularly shaped glia cells resembled more closely the so-called "*gemästete*" glia cells. Only the sixth layer of the parietal cortex was invaded by these cells. The architectural arrangement of the cortical laminae was well preserved. The ganglion cells of the cortex showed no changes, except in the sixth layer, where some were destroyed and others stained poorly. With the Fett Ponceau and sudan IV stains, many of the large, irregularly shaped cells in the white matter were seen to be loaded with fat (fig. 5), as in compound granular corpuscles from areas of softening, infections or degenerative diseases; some of the cells did not contain fat. Some of the substances stained for fat were doubly refractile. With the Cajal and Schultze-Stoehr methods, the large glia cells, which stained black, were irregularly shaped, and some had short processes (fig. 6*A*). The nucleus could not be visualized in the Cajal, Bielschowsky and Schultze-Stoehr stains, but with the silver carbonate stain granules could be seen in these cells, and the nucleus was placed at the periphery. Some glia cells had numerous processes and had the appearance of giant astrocytes. In the Bielschowsky preparations the axis cylinders did not show as marked destructive changes as were seen in the myelin sheaths. In the areas of complete demyelination a few healthy axis cylinders were found. Some of the axis cylinders were fragmented and had a corkscrew appearance; others were slightly swollen (fig. 6*B*). The destroyed areas replaced by glia tissue were best demonstrated by the Holzer and Victoria blue preparations. The large, irregularly shaped glia cells stained deep blue, had processes and were surrounded by glia fibers which had a criss-cross arrangement.

5. A detailed examination of all the organs, except those of the central nervous system, is given in a separate publication (Chester, W., and Kugell, V. H.: Lipoid Granulomatosis [Type, Hand-Schüller-Christian]: Report of a Case, Arch. Path. **14**:595 [Nov.] 1932.

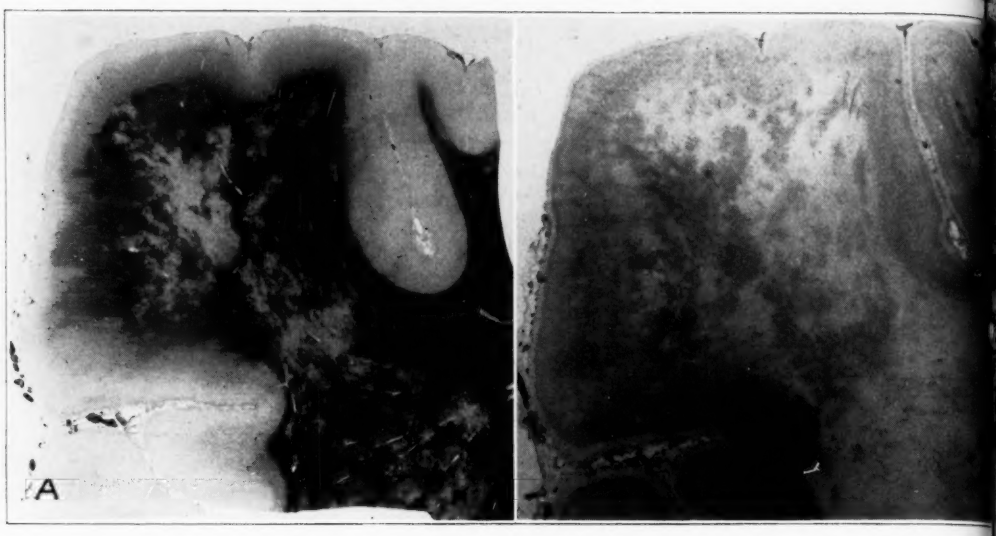

Fig. 3.—*A*, scattered demyelinated plaques in the white matter of the superior parietal convolution. Myelin sheath stain (Weil modification); reduced from magnification × 10. *B*, same as figure 3 *A*, showing the densely stained masses in the white matter. Notice the absence of invasion of the gray matter by these plaques. Cresyl violet stain; reduced from magnification × 10.

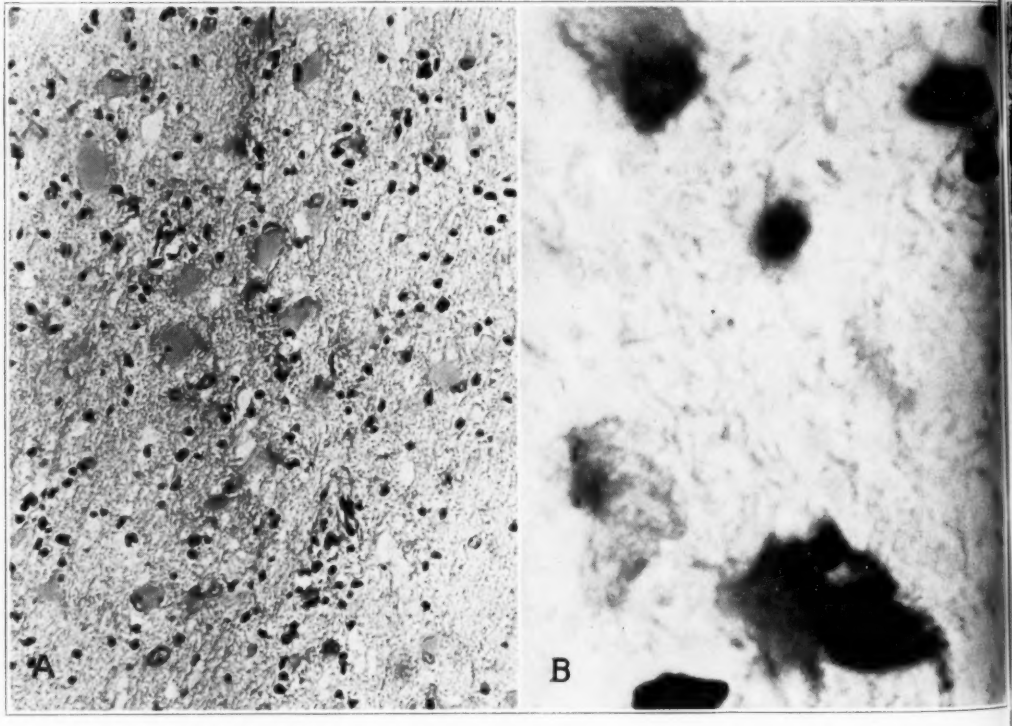

Fig. 4.—*A*, types of giant glia cells from the demyelinated plaques. Notice the pale cytoplasm and deeply stained nucleus at the periphery. Cresyl violet stain; reduced from magnification × 240. *B*, same as figure 4 *A*; reduced from magnification × 900.

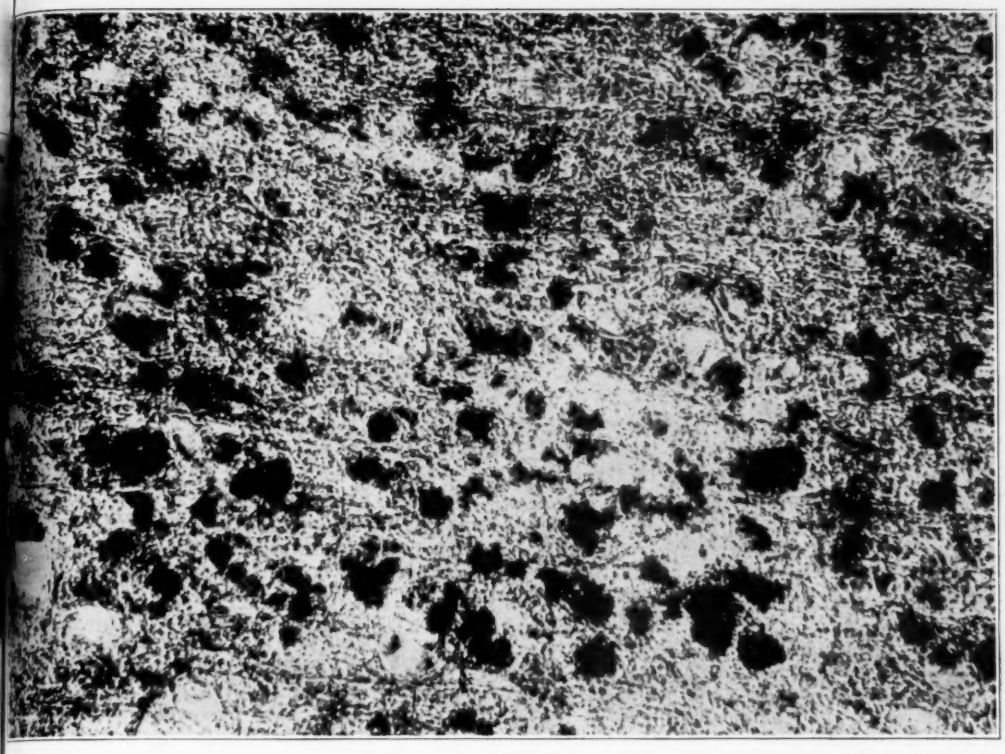

Fig. 5.—Compound granular corpuscles from the demyelinated areas. Sudan stain; × 240.

Fig. 6.—*A*, large glia cells showing short processes. Schultze-Stoehr method; × 480. *B*, partial destruction of axis cylinders in the plaques. The pale bodies represent the giant glia cells in the cresyl violet preparation. Bielschowsky stain; reduced from magnification × 480.

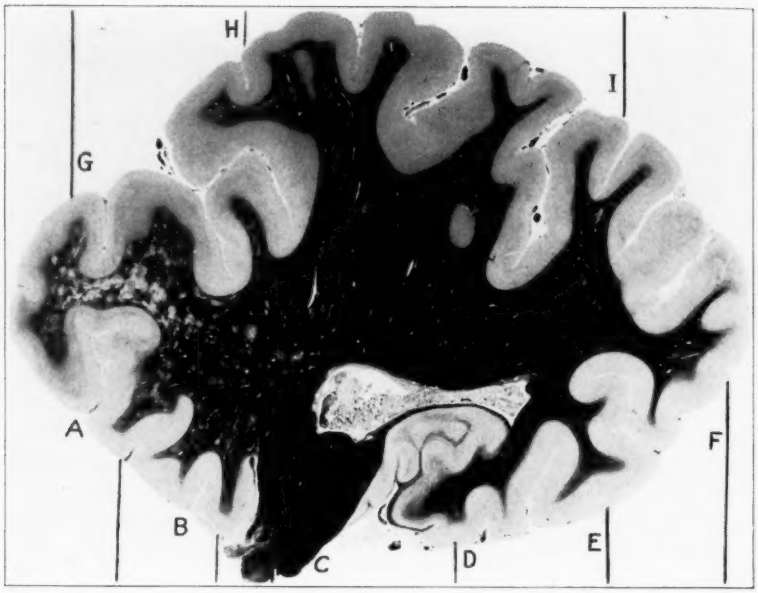

Fig. 7.—Section through the posterior horn of the lateral ventricle showing the demyelinated plaques in the white matter. *A*, paracentral lobule; *B*, cingular gyrus; *C*, splenium; *D*, hippocampal gyrus; *E*, lingual gyrus; *F*, fusiform gyrus; *G*, superior parietal gyrus; *H*, inferior parietal gyrus, and *I*, inferior temporal gyrus.

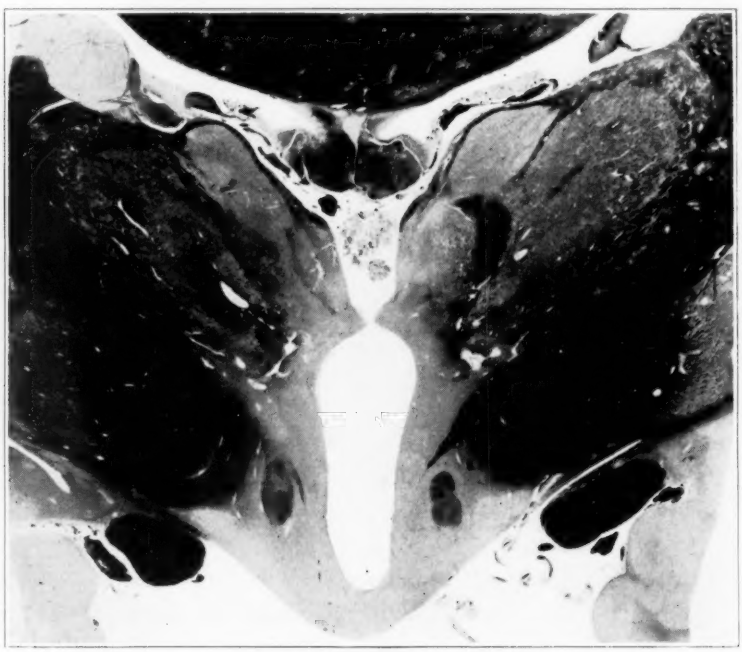

Fig. 8.—Coronal section through the tuber cinereum showing plaques in the corpus callosum and in the internal capsule. With higher power a few plaques were found in the thalamic and striatal nuclei. Myelin sheath stain (Weil modification).

Fig. 9.—Tuber cinereum region. Fibrosis and gliosis. Notice the group of inflammatory cells (indicated by arrow on left). Cresyl violet stain; reduced from magnification × 100.

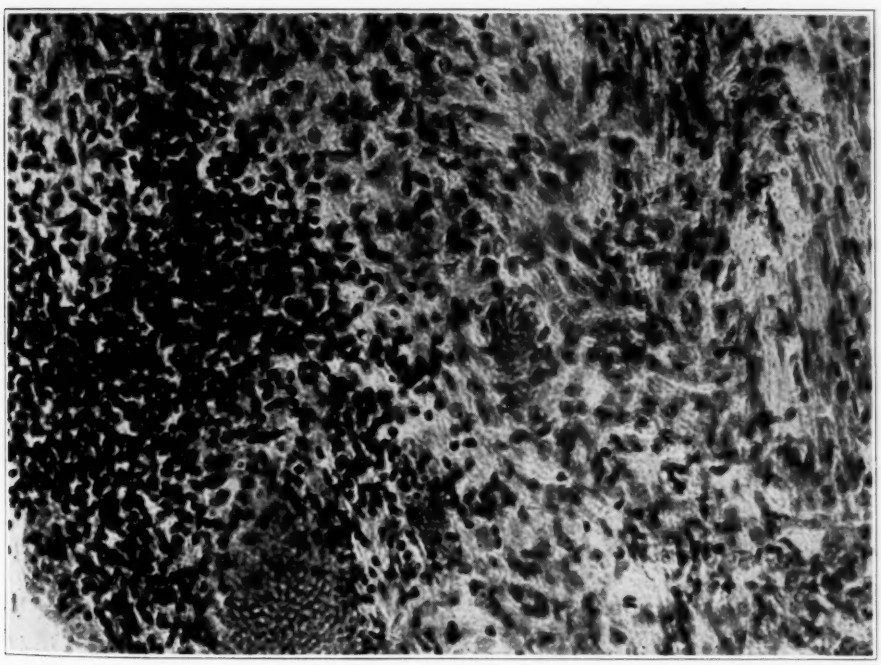

Fig. 10.—Arrangement of the fibroblasts and inflammatory focus in the tuber cinereum. Cresyl violet stain; × 240.

Coronal sections through the posterior horn of the lateral ventricle and other areas showed demyelinated plaques which involved the white matter of the superior and inferior parietal, inferior temporal, hippocampal, dentate and fusiform gyri, the splenium of the corpus callosum and the optic radiation (fig. 7). With cresyl violet and other stains the cells forming the demyelinated plaques had the same histopathologic features as those described in the superior parietal gyrus.

The basal ganglia and tuber cinereum were cut serially. In the myelin sheath sections, numerous small plaques were found scattered throughout the corpus callosum, internal capsule, anterior commissure, thalamus, globus pallidus, fornix and columnae fornices (fig. 8). These plaques consisted of the same type of cells as

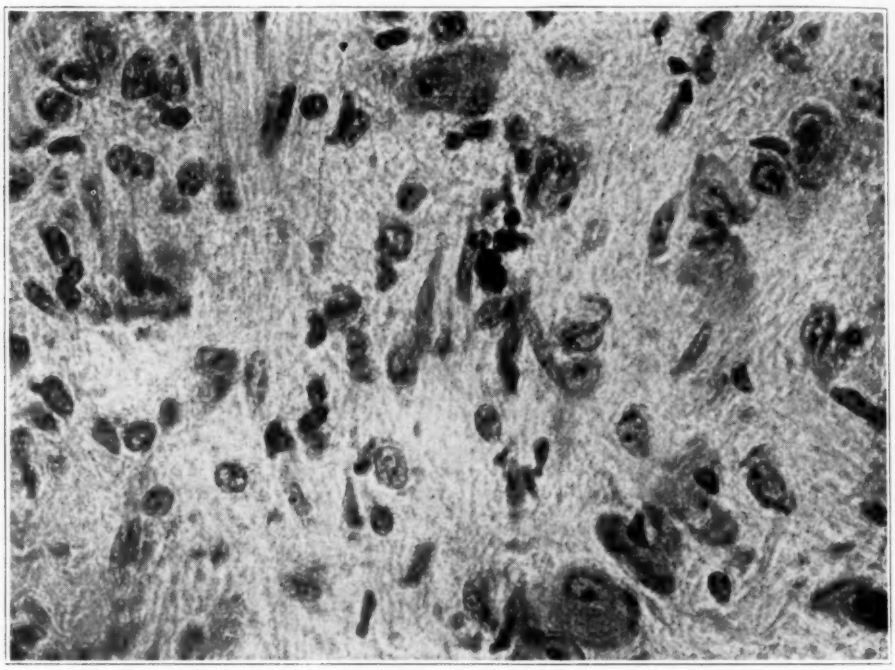

Fig. 11.—Destruction of the ganglion cells of the tuber cinereum and their replacement by connective tissue and glia cells.

those described in the parietal region. In addition, scattered small groups of the same glia cells were found in the globus pallidus, corpus luysii and substantia nigra. Some of the ganglion cells of the thalamus, globus pallidus, corpus luysii and substantia nigra were replaced by these glia cells; others stained poorly and showed signs of beginning disintegration. This process was most marked in the ganglion cells of the corpus luysii and substantia nigra. The ependymal lining of the third ventricle was slightly thickened and had warty outgrowths.

The tuber cinereum was replaced by areas of fibrosis and gliosis, which was best seen in van Gieson preparations. The fibroblasts in some areas had a parallel arrangement, while in others they were in whorls. Lymphocytic infiltrations were found at the periphery (figs. 9 and 10). A few vessels of the tuber cinereum showed perivascular infiltration. There was also new vessel formation. There

were no giant cells. The large glia cells described in the parietal and other regions were few in the tuber. The ganglion cells of the substantia grisea, paraventricular nuclei, nuclei tuberis and nuclei supra-optici were diminished in number; some were destroyed. The cytoplasm in some was pale, without any Nissl substance, and the nucleus was situated at the periphery. Swollen ganglion cells were also observed. Most of the changes were found in the ganglion cells of the substantia grisea and in the nuclei tuberis; these ganglion cells did not contain the pigment found normally, and most of them were replaced or surrounded by fibroblasts (fig. 11).

In the midbrain and pons, sections through the posterior commissure showed small scattered demyelinated plaques in the lateral lemniscus, brachium conjunctivum, medial lemniscus, brachium pontis and pontile fibers. These plaques, as already described, consisted of cells allied to the compound granular corpuscles and to the giant glia cells. The ependyma of the aqueduct was thickened in places. The tissue adjacent to the aqueduct showed a few ependymal nests, some of which looked like multinucleated giant cells. Sections passing through the aqueduct and

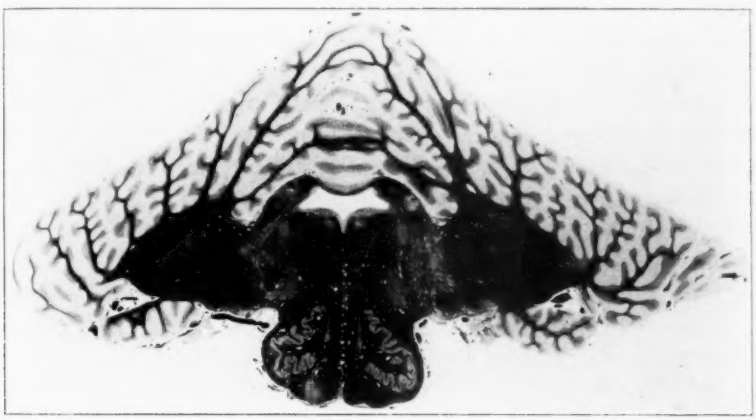

Fig. 12.—Section of the cerebellum and medulla oblongata through the fourth ventricle. Demyelinated areas in the brachium conjunctivum and pontis and in the right pyramid. Closer observation reveals slight areas of demyelination in the cerebellar fibers. Myelin sheath stain (Weil modification).

the origin of the trigeminus disclosed small plaques in the decussation of the brachium conjunctivum, the left sensory nucleus of the fifth nerve and in the right and left fifth nerve as they emerged from the pons. The ganglion cells of the left fifth sensory nucleus were diminished in number; some showed poor chromatin material, while others were completely destroyed.

Sections of the cerebellum and medulla oblongata through the tenth and twelfth nuclei revealed numerous demyelinated plaques in the brachium pontis, brachium conjunctivum, posterior longitudinal bundle and right pyramid (fig. 12). The histopathologic process was the same as in the previous sections.

COMMENT

Clinical Picture.—The clinical picture of the disease process, unlike many of the cases, started when the patient was 22, with pain and falling out of the teeth. Deposition of granulomatous tissue in various

organs soon followed, accompanied by symptoms referable to these organs. Three years later, diabetes insipidus was first noticed. At the age of 28, a few neurologic symptoms and signs appeared—horizontal nystagmoid twitches and loss of taste over the left anterior two thirds of the tongue. The neurologic signs progressed, and, two years after their appearance, there developed involvement of the pyramidal tracts, cerebellum, left sensory fifth nerve and left peripheral facial nerve, and slight involvement of the eighth nerve. The cholesterol content of the blood serum was normal; the total fat was increased. These findings led to the suspicion that the granulomas infiltrated the hypophysis, the hypothalamus, the sensory nucleus of the fifth nerve and the cerebellum.

The condition in this patient, except for the lack of exophthalmos, conforms to the cardinal signs of the Schüller-Christian syndrome, i. e., defects in the membranous bones, exophthalmos and diabetes insipidus. The absence of exophthalmos was due possibly to the lack of invasion of the retrobulbar tissues by the lipoid granuloma. As in most cases of Schüller-Christian disease, the bony changes were not confined to the skull but were found also in other parts of the skeletal system. These changes as demonstrated were predominantly osteoclastic, although evidence of osteoplastic changes was also reported.

Pathology.—Grossly, except for the slight spongy appearance of the parietal regions, the brain was normal. Histopathologically, however, numerous demyelinated plaques were found in the white matter of most of the convolutions, but were more noticeable in the superior and inferior parietal, inferior temporal, hippocampal and fusiform gyri (fig. 7). The optic radiation, corpus callosum, internal capsule, thalamus, globus pallidus, corpus luysii, substantia nigra, lemnisci, brachium conjunctivae, brachium pontis, cerebellum and pyramids were also involved. These plaques were filled with large glia cells containing a pale cytoplasm and a deeply stained nucleus placed at the periphery. The plaques existed essentially in the white matter. A few collections were found in the gray matter of the thalamic nuclei, paleostriatum and in the sixth cortical layers. Occasional multinucleated cells were also found. Some of the giant cells contained fat and resembled compound granular corpuscles. The others had the same structures as the *gemästete* glia cells. Some of the substances stained with fat were doubly refractile.

The capsule of the hypophysis was invaded by the typical foam cells. The tuber cinereum, in addition to a few scattered giant glia cells, was the seat of an intense fibrosis, gliosis and a slight inflammatory process (figs. 9 and 10). The ganglion cells of the nuclei of the tuber cinereum were diminished in number, and those that escaped destruction showed pathologic changes varying in degree.

The essential pathologic process consisted of patchy destruction of the myelin sheaths, of the axis cylinders and of the ganglion cells of the tuber cinereum. The ganglion cells of the other structures, except those of the sixth layer in the parietal region, were spared. The destroyed areas were replaced by compound granular corpuscles and giant glia cells or *gemästete* glia cells (fig. 4).

It is remarkable that in most of the plaques both compound granular corpuscles and giant glia cells were found. The cells which resembled the *gemästete* glia cells, as is well known, originate from the plasma giant cells (astrocytes), while the compound granular corpuscles are derivatives of the microglia. It is difficult to state with certainty whether these cells are in any way related to the lipoid foam cells found in other organs. The compound granular corpuscles perhaps have some relation to the foam cells. I am inclined to consider the other glia cells in the same category as the fibrosis, which is frequently associated with the lipoid foam cells in other tissues. These glia cells may at first have been true lipoid cells, perhaps compound granular corpuscles (some could still be identified as such), which eventually were removed from the areas of destruction and replaced by the large glia cells. The gliosis in a certain sense may be compared with fibrosis, a replacement seen in tissues in this or other conditions. Extensive fibrosis and gliosis were, however, observed only in the tuber cinereum. Less intensive gliosis was also observed in other plaques. The *gemästete* glia cells, as is well known, are found in regions of arteriosclerotic scars and especially in regions where nerve tissue is destroyed. In diffuse processes they are less often seen. The same type of cell is seen in amaurotic family idiocy and in Niemann-Pick's disease. The protoplasm of the *gemästete* glia cells is homogeneous and may often contain vacuoles; the presence of the vacuoles depends on whether or not the condition is of regressive form. Now and then one sees lipoid material, though the contents of these cavities do not give a chemical color reaction. Many of the *gemästete* elements disintegrate or conglomerate, but between their nuclei the pale cytoplasm can be seen. In contrast to neuronophagia, according to Spielmeyer,[6] this can be called gliophagia. It has been demonstrated that the microglia are the phagocytic elements in the brain, and are the source of the macrophages of the central nervous system. In destruction of nerve tissue, the microglia immediately multiply, enlarge, lose their processes and become ameboid phagocytes. These are the compound granular corpuscles, scavenger cells or gitter cells. Some persons have suggested that the microglia is the third element or the reticulo-endothelial cell of the nervous system. If these views can be accepted, the compound granular corpuscles in the

6. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer, 1922, p. 177.

central nervous system in my case can be placed in the same group as the foam cells, which according to Rowland and others take their origin from the reticulo-endothelial cells.

General Clinical Considerations.—The symptom triad described in this paper has been observed to date in forty-nine cases, including the case reported in this article. The disease in this patient showed some striking differences from the usual picture. A brief general review of the disease process and an attempt to bring out some differential points will be made.

Age, Sex and Race: As will be seen in the accompanying table, in thirty-three of forty-nine cases the disease started in the first decade of life; in three in the second; in eight in the third; in one in the fourth; in two in the fifth, and in one in the seventh. Niemann-Pick's disease and amaurotic family idiocy, which also represent disturbances in lipoid metabolism, have the same predilection for the early years of life. Gaucher's disease, however, may occur at any age; it generally begins in infancy and has a chronic course. Males are more frequently affected than females. In the forty-nine cases there were thirty-two males and seventeen females. The disease has no preference for the Jewish race, as has commonly been observed in splenohepatomegaly or amaurotic family idiocy. There is no hereditary basis for the disease; it occurred in the same family only in Rowland's [7] and in Herzenberg's [8] cases.

Diagnostic Features: The most important symptoms are swelling and defects in the bones of the skull, exophthalmos and diabetes insipidus. Defects in the bones of the skull were present in all cases except the two of Chester.[9] Pusey and Johnston,[10] Spillman and Watrin,[11] and Turner, Davidson and White [12] did not mention whether or not the bones of the skull were involved. The swellings and defects in the bones are most frequent in the region of the parietal bones, sella turcica and orbits. Diabetes insipidus, which is next in frequency, occurred in thirty-six cases. Exophthalmos was present in thirty cases. Gingivitis and defective teeth were recorded in seventeen cases. Decrease in

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7. Rowland, R. S.: Xanthomatosis and the Reticulo-Endothelial System (Christian's Syndrome), Arch. Int. Med. **42**:611 (Nov.) 1928.

8. Herzenberg, H.: Die Skelettform der Niemann-Pickschen Erkrankung, Virchows Arch. f. path. Anat. **269**:614, 1928.

9. Chester, W.: Ueber Lipoidgranulomatose, Virchows Arch. f. path. Anat. **279**:561, 1930.

10. Pusey, W. A., and Johnston, O. P.: A Case of Xanthoma Diabeticorum and Lipoma Multiplex and a Case of Xanthoma Approaching the Diabetic Type with Diabetes Insipidus, J. Cutan. Dis. **26**:522, 1908.

11. Spillman, L., and Watrin, J.: Contribution à l'étude du xanthome papuleux générale, Paris méd. **10**:193, 1920.

12. Turner, A. L.; Davidson, J., and White, A. C.: Xanthomatosis: Some Aspects of Its Blood Chemistry and Pathology, Edinburgh M. J. **32**:153, 1925.

growth and mental development were noted in about half of the cases. The secondary retrogressive sexual characteristic belonging to the dystrophia adiposogenitalis group were also observed in a few of the cases. A number of the cases showed (table) increase in blood cholesterol and total fat. The case reported showed only an increase in total fat; the blood cholesterol was within normal limits. As the chemical studies were made in only a small number of the cases, one should be guarded in considering hypercholesteremia as a definite diagnostic criterion.

Neurologic Findings and Autopsy Reports: Records of neurologic symptoms and signs, in addition to diabetes insipidus, are to be found in the cases of Dietrich,[13] Veit,[14] Thompson, Keegan and Dunn,[15] Kyrklund,[16] Herzenberg,[8] Chiari [4] and in my case. Changes in the dura as observed at autopsy were recorded in the cases mentioned and in those of Griffith (Weidman-Freeman) and Rowland (table). The only cases reported in which the study of the neural structures received special attention are those described by Thompson, Keegan and Dunn,[15] Kyrklund,[16] and Weidman and Freeman [17] (Griffith's case).

In Dietrich's case the hypophysis and optic nerves were surrounded by tumor masses. The optic nerves, however, showed no atrophic changes, nor were they actually infiltrated by foam cells. The ciliary ganglion showed a network of fibrillae, numerous connective tissue fibers, with foam cells. Veit found changes in the hypophysis; the brain was not studied. Weidman and Freeman found xanthic changes in the pineal body and tuber cinereum, which were more marked at the periphery. The reaction observed in the brain was glial, and the cortical ganglion cells were not extensively damaged. Patches of degenerated cells in the tuber cinereum were identified as glia cells. The authors thought that some of the cells belonged to the xanthoma type, but concluded that the nerve tissue is refractory to xanthic change, just as it is immune to fatty infiltration. Thompson, Keegan and Dunn described in their cases definite findings in the nerve portion of the pituitary gland and in the tuber cinereum. Except for an inflammatory reaction of the adjacent brain tissue near the tuber, pathologic changes in the rest of

13. Dietrich, A.: Ueber ein Fibroxanthosarcom mit eigenartiger Ausbreitung und über eine Vena cava supra sinistra bei dem gleichen Fall, Virchows Arch. f. path. Anat. **212**:119, 1913.

14. Veit: Ein Beitrag zur pathologischen Anatomie der Hypophyse, Frankfurt. Ztschr. f. Path. **28**:1, 1922 (Hochstetter's case).

15. Thompson, C. O.; Keegan, J. J., and Dunn, A. D.: Defects of Membranous Bones, Exophthalmos and Diabetes Insipidus, Arch. Int. Med. **36**:650 (Nov.) 1925.

16. Kyrklund, R.: Beitrag zu einem seltenen Symptom-Komplex, Ztschr. f. Kinderh. **41**:56, 1926.

17. Weidman, F., and Freeman, W.: Xanthoma Tuberosum, Arch. Dermat. & Syph. **9**:149 (Feb.) 1924.

Cases Recorded in the Literature

No.	Author	Age, Years	Sex	Signs, Symptoms and Blood Cholesterol	Changes in Bones of Skull	Autopsy and Central Nervous System Changes
1.	Schüller (1915)[2a]	12	M	Exophthalmos, dystrophia adiposogenitalis, nycturia	+	—
2.	Schüller (1915)[2a]	2	F	Exophthalmos, polyuria	+	—
3.	Schüller (1926)[2b]	5	F	Bilateral exophthalmos, diabetes insipidus	+	—
4.	Christian (1919)[3]	3	F	Gingivitis, exophthalmos, polyuria, polydipsia; cholesterol, 129 mg. % (1930)	+	—
5.	Hand (1905)[1]	4	M	Gingivitis, falling out of teeth, exophthalmos, polyuria, polydipsia, swelling of head	+	—
6.	Hand (1906)[1]	2	M	Bilateral exophthalmos, polyuria, polydipsia, bronzing of skin	+	Yellow masses found in skull
7.	Pusey and Johnston (1908)[10]	14	M	Polyuria, polydipsia, dizziness, fainting and hoarseness	No mention of defects in the bones	—
8.	Dietrich (1913)[13]	25	F	Exophthalmos, Basedow's disease, pleural effusion, no mention of polyuria	+	Yellow masses found in the walls of the longitudinal sinus, sinus transversus, cavernosus and in region of sella; optic nerves also surrounded by these masses
9.	Spillman and Watrin (1920)[11]	7	M	Diabetes insipidus	Tumor masses about the eyelids and over entire body, but nothing is said of the bones of the skull	—
10.	Veit (1922)[14]	38	M	Falling out of teeth, eczema, xanthomas in both eyelids, diabetes insipidus, headache, polyneuritis, anemia; blood cholesterol, 174 mg. %	+	Lipoid deposits in the dura, hypophysis and bones of sella turcica
11.	Griffith (1922)[17]	3	F	Defective teeth, exophthalmos, diabetes insipidus; blood cholesterol, 397 mg. %	+	Yellowish masses in the dura, in the vicinity of the hypophysis, tuber cinereum and other organs
12.	Grosh and Stiffel (1923): Defects in Membranous Bones: Diabetes Insipidus and Exophthalmos, Arch. Int. Med. **31**: 76 (Jan.) 1923	6	F	Gingivitis, falling out of teeth, left exophthalmos, diabetes insipidus	+	—
13.	Alberti (1924): Radiol. med. **11**: 517, 1924	13	M	Exophthalmos, diabetes insipidus; dwarf; had ceased to grow after 13; seen by author when 21 years of age	+	—
14.	Schoen (1924): Deforming Ostetis with Diabetes Insipidus, München. med. Wchnschr. **71**: 1713, 1924	26	F	Diabetes insipidus, headache, dizziness	+	—

15. Schultz, Wermbter and Puhl (1924): Eigentümliche granulomartige Systemerkrankung des hämopoetischen Apparates, Virchows Arch. f. Path. Anat. **252**: 519, 1924	2	F	No mention made of exophthalmos or diabetes insipidus, headache and swelling of skull; enlarged liver and spleen	+	Nodules were found all over; no mention made of changes in the hypophysis or brain
16. Berkheiser (1924): Multiple Myelomas of Children, Arch. Surg. **8**: 853 (May) 1924	3½	F	Exophthalmos, nycturia	+	Biopsy showed the tumor to be xanthoma
17. Thompson, Keegan and Dunn (1925)[15]	7½	M	Gingivitis, falling out of teeth, exophthalmos, polyuria, polydipsia, poorly developed genitalia, yellow discoloration of skin	+	Changes were found in the region of the hypophysis and tuber cinereum
18. Turner, Davidson and White (1925): Xanthomatosis, Edinburgh M. J. **32**: 153, 1925	22	F	Diabetes insipidus, rash, huskiness of voice; blood cholesterol, 181 mg. %	Nothing said of defects of the bones of the skull except a raised brownish, firm eruption on the forehead	Lipoid cells in most of the organs; pituitary gland invaded by lipoid cells; nothing said of brain
19. Gilmore (1925): Multiple Myeloma Syndrome in a Child, Texas State J. Med. **21**: 358, 1925	1	F	Unilateral exophthalmos; when 1 year of age, collapse of second lumbar vertebra; considered by Gilmore as multiple myeloma	+	—
20. Kyrklund (1926)[16]	4	F	Carious teeth, exophthalmos, polyuria, defective mentality	+	Soft masses in the defects of the calvarium and hypophyseal region
21. Denzers (1926): Defects in the Membranous Bones, Diabetes Insipidus and Exophthalmos, Am. J. Dis. Child. **31**: 480 (April) 1926	4½	M	Gingivitis, carious teeth, exophthalmos, polyuria, polydipsia	+	—
22. Heard, Schumacher and Gordon (1926): Association of Diabetes Insipidus with Osteitis Fibrosa Polycystica, Am. J. M. Sc. **171**: 38, 1926	2	M	Diabetes insipidus, head injury, swelling followed by similar involvement of other bones	+	—
23. Stowe (1927): Case of Diabetes Insipidus Associated with Defects in the Skull, M. J. Australia **5**: 144, 1927	Unknown	M	Exophthalmos, diabetes insipidus.....	+	—
24. Rowland (1928)[7]	3	M	Gingivitis, falling out of teeth.....	+	In addition to yellow nodules found in most of the organs, the body of the first lumbar vertebra also involved; no changes in the brain
25. Rowland (1928)[7]	2	M	Slight exophthalmos, polyuria, polydipsia, sleepiness; blood cholesteral, 315 mg. %	+	—
26. Herzenberg (1928)[8]	4	F	Polyuria, enlargement of lymph glands, dry skin, severe anemia, pains in legs, arms and shoulders, edema of face and fever	+	Masses in the bones, dura and infundibulum; Herzenberg considered this a case of Niemann-Pick's disease

Cases Recorded in the Literature—Continued

No.	Author	Age, Years	Sex	Signs, Symptoms and Blood Cholesterol	Changes in Bones of Skull	Autopsy and Central Nervous System Changes
27.	Hausman and Bromberg (1929): Diabetic Exophthalmos Dysostosis, Arch. Neurol. & Psychiat. **21**: 1402 (June) 1929	2	M	Bilateral exophthalmos, diabetes insipidus	+	—
28.	Wassilyeff (1929): Eine eigenartige Form der Knochenmarksystem Erkrankung mit Osteosclerosis, Virchows Arch. f. path. Anat. **271**: 134, 1929	25	M	Pains in the joints, nasal hemorrhages, no mention of exophthalmos or diabetes insipidus	+	Lipoid cells in most of the organs, but nothing said of the brain
29.	Pickhan and Joel (1929): Zur Frage des sogenannten Lautkartenschädels, Röntgenpraxis **1**: 791, 1929	3½	M	Falling out of teeth, exophthalmos, swelling of temporal bones	+	—
30.	Globig (1929): Ueber eine eigenartige Knochenerkrankung mit multipler Tumorbildung im Skelettsystem, bei einem Kinde, Jahrb. f. Kinderh. **125**: 90, 1929	3	M	Soft swelling of the head, no mention of exophthalmos or diabetes insipidus, pains in the hips	+	—
31.	Cignolini (1929): Effetti locali e generali della radioterapia in un caso di diabete insipido associato ad osteopatio, Radiol. med. **16**: 16, 1929	2	M	Gingivitis, diabetes insipidus.....	+	—
32.	Hofer (1930): Beitrag zur Xanthomatose der Dura mater und der Schädelknochen, Klin. Wchnschr. **9**: 1302, 1930	4	M	Left exophthalmos, polydipsia, poorly developed genitalia; blood cholesterol, 238 mg. %	+	Biopsy; typical xanthoma
33.	Henschen (1930): Fall von Xanthomatose mit Knochenveränderungen und grosszelliger Splenomegalie, Centralbl. f. allg. Path. u. path. Anat. **50**: 44, 1930	2	F	Falling out of teeth, diabetes insipidus, eczema	+	Nothing said about findings in the brain; the lipoid masses were seen in other organs
34.	Sophian (1930): Diabetes Insipidus and Osteitis Fibrosa Polycystica, J. A. M. A. **95**: 483 (Aug. 16) 1930	25	M	Defective teeth, diabetes insipidus, impotence, loss in weight, generalized eczema	+	—
35.	Schotte (1930): Ueber eine Systemserkrankung des Skeletts, Klin. Wchnschr. **9**: 1826, 1930	2	F	When 2 years of age swellings of the head, which disappeared in from three to four months; no diabetes insipidus	+	—
36.	Cohen, Moreau and Murdoch (1930): La dysostose hypophysaire xanthomatose des os du crane, Rev. d'orthop. **17**: 714, 1930	2¼	M	Exophthalmos, no diabetes insipidus	+	—

37. Vampré (1930): Syndrome de Christian, Rev. sud. am. de méd. et de chir, **1**: 459, 1930	4	M	Exophthalmos, polyuria, polydipsia, hypogenitalism	+	—
38. Rothnem (1930): Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus, Radiology **15**: 694, 1930	2	M	Exophthalmos, polyuria, polydipsia	+	Biopsy report: infectious process and giant cell tumor; died; no autopsy obtained
39. Chester (1930)[9]	44	F	Three years before death xanthoma of both eyelids; blood cholesterol, 95 mg. %	Defects in the bones of the skull not found	Changes found in most of the organs, especially the skeletal system; the brain not examined
40. Chester (1930)[9]	69	M	Xanthoma in upper eyelids	Defects in the bones of the skull not found	Changes found in many organs; neural structures not examined
41. Chiari (1931)[4]	26	M	Exophthalmos, sluggish reaction of pupils to light, slight weakness of right side of face, hypogenitalism; margins of disks not clear and right papilla swollen; slight neurotic atrophy on the left; blood cholesterol, 192 mg. %	+	Lipoid masses found in the dura, falx tentorium and region of the hypophysis; edema of the brain and in retrobulbar tissue; in the neurohypophysis, granulation tissue and lymphocytic infiltration extending as far as the tuber cinereum
42. Frehman, Dahl and Frosberg (1931): Xanthomatosis with Cranial Defects, Norsk mag. f. laegevidensk. **92**: 523, 1931	8	F	Left exophthalmos, polyuria, polydipsia, retardation of growth, pain in left temporal region following trauma, high blood cholesterol	+	—
43. Sossman (1932): Xanthomatosis (five cases), J. A. M. A. **98**: 110 (Jan. 9) 1932	4	M	Exophthalmos, polyuria, polydipsia; blood cholesterol, 131.7 mg. %	+	—
44. Ibid.	41	M	Diabetes insipidus, dizziness and staggering, choked disks, erysipelas, discharge from the ear	+	—
45. Ibid.	2	M	Gingivitis, exophthalmos, diabetes insipidus, loss in weight; blood cholesterol, between 193 and 200 mg. %	+	—
46. Ibid.	2½	M	Falling out of teeth, exophthalmos, no diabetes insipidus; blood cholesterol, 170 mg. %	+	—
47. Ibid.	2	M	Exophthalmos, diabetes insipidus, loss of voice; blood cholesterol, 191 mg. %	+	Biopsy: "foam cells"
48. Kartagener and Fischer (1932): Untersuchungen über den Lipoid und Calcium Stoffwechsel in einem Fall von Schüller-Christianischer Krankheit, Ztschr. f. klin. Med. **119**: 422, 1932	23	M	Defective teeth, left exophthalmos, diabetes insipidus, hypogenitalism; blood cholesterol, between 148 and 164 mg. %	+	—
49. Davison (1932)	22	M	Falling out of teeth, diabetes insipidus, scattered neurologic signs; blood cholesterol, 152 mg. %	+	Changes in most organs, also in the hypophysis, tuber cinereum and central nervous system

The ages given are whenever possible those at the onset of the illness.

the nervous system were not mentioned. The anterior part of the pituitary gland in their cases showed an inflammatory reaction, in contrast to the typical foam cells found in my case. The authors considered the clinical and the histopathologic observations as an inflammatory rather than a degenerative or primary metabolic process. They are opposed to the view that either the anterior or the posterior lobe of the pituitary gland has any rôle in pathogenesis. In view of the polyuria experimentally induced by lesions in the tuber cinereum, the authors are willing to attribute the diabetes insipidus to lesions of the hypothalamus. Kyrklund did not demonstrate any changes in the hypophysis and tuber cinereum in his case, but mentioned some indefinite perivascular infiltrations in the brain. In Rowland's case, granulomas surrounded the hypophysis and destroyed the sella turcica. The brain did not show any changes. Herzenberg described masses in the calvarium, dura and infundibulum. The hypophysis and dura showed the typical foam cells. Changes were not found in the brain substance. Chiari found masses in the falx, tentorium, hypophysis and retrobulbar tissue. There were granulation tissue and lymphocytic infiltration in the neurohypophysis; these extended as far as the tuber cinereum. The cases of Thompson, Keegan and Dunn, and Weidman and Freeman are the only examples of neural changes, although none of them approached the extensive involvement of practically the entire nervous system that was found in this case.

Pathologic Considerations.—Many theories have been advanced to explain the causation of this symptom triad. The disease has been considered neoplastic, traumatic and inflammatory, and of late it has been considered a lipoid metabolic disorder.

The supporters of the neoplastic theory drew conclusions from the character and deposition of the tumor-like masses in various organs. Kyrklund and Dietrich considered the tumors as sarcomatous growths; Dietrich believed that they are malignant tumors which metastasize. Some authors go a step further, and state that the neoplasm is secondary to trauma. This is not wholly unwarranted, since in many cases the swellings in the head or elsewhere followed some trauma to those structures.

Others believe the lesion to be inflammatory. The frequent appearance of the masses following some intercurrent infection in childhood, such as measles, scarlet fever and whooping cough, and histopathologic changes of inflammatory foci and fibrosis in conjunction with the deposition of the lipoid cells are brought forth as evidence of an inflammatory process. Some authors considered the lipoid granulomas as a neoplasm of connective tissue. The inflammation is considered primary, and the fibrosis and the neoplasm as secondary, to some toxic or infectious agent.

The more recent studies on this subject consider the disease due to disturbances in lipoid metabolism and allied to Gaucher's or Niemann-Pick's disease and amaurotic family idiocy. The double refractile bodies in the fat-filled cells, the high cholesterol content in the dural plaques and the frequently high percentage of cholesterol and total fat in the blood of these patients are the main support of the latter theory.

Amitschow [18] and others succeeded in reproducing xanthoma by feeding rabbits on diets rich in cholesterol. The organs of these animals, especially the splenic pulp, lymph nodes, bone marrow, Kupffer cells of the liver and the walls of the larger vessels, were stored with foam cells loaded with cholesterol esters. According to Amitschow, the xanthoma is characterized by the formation of xanthoma cells and the proliferation of connective tissue.

Pick,[19] following his investigations of Niemann-Pick's disease, came to the conclusion that the lipoid cell is of primary constitutional origin and represents a familial disturbance in lipoid metabolism. In splenohepatomegaly the deposits consist of phosphatids which are not doubly refractile. These are supposed to originate from the reticular cells, but, according to some authors, Knox, Wahl, Schmeiser [20] and others, they are also found in the endothelial cells of the sinus. In Gaucher's disease the lipoid content of the cells consists of kerasin instead of phosphatids, as found in Niemann-Pick's disease or cholesterol, as in the Schüller-Christian syndrome. In Gaucher's disease, the lipoid cells originate from the reticular cells in the spleen, liver and lymph glands, and in small number from the clasmatocytes in the adventitia of the small splenic arteries and the central veins of the lobules of the liver.

In addition to the differences in the type of lipoid, there are also some clinical points of differentiation worth recording.

Gaucher's disease may occur at any age; it generally begins in infancy, and usually pursues a chronic course. It is familial in about half of the cases. The lipoid in the form of kerasin, although mainly deposited in the spleen, may be found also in other parts of the reticuloendothelial system.

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18. Amitschow: Ueber experimentelle erzeugte Ablagerungen von anisotropen Lipoidsubstanzen in der Milz und im Knochenmark, Beitr. z. path. Anat. u. z. allg. Path. **27:**201, 1914.

19. Pick, L.: Die Histio- und Pathogenese des Morbus Gaucher, seine histio- und pathogenische Abgrenzung von ähnlichen Krankheitszuständen, insbesondere der lipoidzelligen Splenohepatomegalie (Typus Niemann-Pick), Med. Klin. **20:** 1526, 1924; Ueber die lipoidzellige Splenohepatomegalie, Verhandl. d. Gesellsch. f. Verdauungs-u. Stoffwechselkr. **8:**134, 1929.

20. Knox, G. H. M.; Wahl, W. H., and Schmeiser, H. C.: Gaucher's Disease; A Report of Two Cases in Infants, Bull. Johns Hopkins Hosp. **27:**1, 1916.

Niemann-Pick's disease occurs mainly in Jewish infants; females are more frequently attacked than males, and the disease has an acute, rapid and fatal course. In this disease the organs chiefly involved are the liver and spleen, which become enormously enlarged. As already demonstrated by others, the lipoid deposits may be found in all organs, as well as in the nervous system, as has been described by Bielschowsky [21] and Hassin.[22] Bielschowsky believed that there is a definite clinical relationship and an analogous disturbance in lipoid metabolism in Niemann-Pick's disease and in amaurotic family idiocy. As Sachs [23] and Hassin pointed out, however, striking visceral changes observed in Niemann-Pick's disease have not yet been found in amaurotic family idiocy. More material from such cases will have to be studied before a definite relationship is established. I am studying a case of amaurotic family idiocy in which the visceral organs showed lipoid accumulations. At present it is safe to say that the two conditions are associated with disturbances in lipoid metabolism.

In xanthomatosis the disease, as already demonstrated, occurs mostly in males, preponderantly in the first and second decade of life, and has a slow course. Remissions may occur. The lipoid deposits, cholesterol, are found mainly in the membranous bones, although the deposits may be found in other organs. The lipoid "foam cells" constitute the main feature of the granuloma. In addition, associated reactive phenomena consisting of inflammatory cells and fibrosis are also found. It may be assumed that the lipoid cells originate from the mesenchyme or are exudative cells which may become filled with fat and appear as foam cells. The exudative cells generally consist of lymphocytes, eosinophils and plasma cells.

In the central nervous system, as demonstrated in this case, the compound granular corpuscles, derivatives from the microglia cells (the third element or reticulo-endothelial cells of the nervous system), are the same as the foam cells found in other organs. The giant glia cells or *gemästete* glia cells, derivatives of the astrocytes, correspond to the connective tissue cells found in the areas of fibrosis. In other words, a twofold process was found in the nervous system: deposition of fat cells and a reparative process—gliosis—consisting primarily of giant glia cells. In contrast to Niemann-Pick's disease and amaurotic family idiocy, the ganglion cells in this case were not swollen, did not show deposits of lipoid and were not extensively involved. The most important changes were not found in the gray but in the white matter.

21. Bielschowsky, M.: Amaurotische Idiotie und lipoidzellige Splenohepatomegalie, J. f. Psychol. u. Neurol. **36**:103, 1928.

22. Hassin, G. B.: Niemann-Pick's Disease, Arch. Neurol. & Psychiat. **24**:61 (July) 1930.

23. Sachs, B.: Amaurotic Family Idiocy and General Lipoid Degeneration, Arch. Neurol. & Psychiat. **21**:247 (Feb.) 1929.

Physiologic Considerations.—Although the mechanism of the triad of symptoms—defects in the membranous bones, exophthalmos and diabetes insipidus—is still speculative, it is interesting to discuss. As already mentioned, a number of the cases in which necropsy was performed showed definite deposits of the granulomatous masses in the region of the hypophysis and tuber cinereum. In some cases the hypophysis was actually infiltrated by the lipoid cells, and in the cases of Thompson, Keegan and Dunn, Weidman and Freeman and in my case the tuber cinereum also showed inflammatory changes, fibrosis and gliosis.

At one time the diseased hypophysis was considered the organ solely responsible for the production of diabetes insipidus. Aschner's [24] investigations on glycosuria, those of Leschke and Schneider [25] on water metabolism, and those of Camus and Roussy,[26] Bailey and Bremer [27] and others on polyuria demonstrated the existence of vegetative centers in the tuber cinereum. The experimental as well as the clinical data lead one to believe that the hypophysis and the hypothalamus are one unit. Kary [28] destroyed the hypophysis and traced degeneration in the gray matter of the tuber cinereum and in the nucleus supra-opticus. Pines contended that the posterior half of the hypophysis contains fibers coming from the lateral part of the base of the diencephalon. Greving [29] stated that the posterior lobe of the pituitary gland is in connection with the nucleus supra-opticus by means of the tractus supra-opticus hypophyseus. The anterior and middle lobes did not have fibers of this tract. Mainman,[30] after destroying the posterior and middle lobes of the hypophysis in dogs, demonstrated degeneration in the nucleus supra-opticus alone; the nerve cells of the nucleus supra-opticus showed chromatolysis. It is therefore safe to accept the view that the middle and posterior lobes of the hypophysis are innervated by the nucleus supra-opticus. The anterior lobe is said to receive its nerve supply from the carotid plexus.

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24. Aschner, B.: Zur Physiologie des Zwischenhirns, Wien. klin. Wchnschr. **25**:1042, 1912.

25. Leschke, E., and Schneider, E.: Ueber den Einfluss des Zwischenhirns auf den Stoffwechsel, Ztschr. f. exper. Path. u. Therap. **19**:58, 1918.

26. Camus, J., and Roussy, G.: Les functions attribuées à l'hypophyse, J. de physiol. et de path. gén. **20**:509 and 535, 1922.

27. Bailey, P., and Bremer, F.: Experimental Diabetes Insipidus, Arch. Int. Med. **28**:773 (Dec.) 1921.

28. Kary, K.: Pathologisch-anatomische und experimentelle Untersuchungen zur Frage des Diabetes insipidus und der Beziehungen zwischen Tuber Cinereum und Hypophyse, Virchows Arch. f. path. Anat. **252**:734, 1924.

29. Greving, R.: Zur Anatomie und Pathologie der vegetativen Zentren in Zwischenhirn, Ztschr. f. d. ges. Anat. **3**:348, 1922.

30. Mainman, R. M.: Ueber die Zentren der Hypophysis cerebri, Ztschr. f. d. ges. Neurol. u. Psychiat. **129**:666, 1930.

In view of what was stated, it is definitely established that the diabetes insipidus is the end-result of pathologic changes in the hypophysis-tuber region. Whether the same neural centers are directly responsible for the generalized lipoid metabolism is more difficult to state. One may further speculate that a vicious circle is established by the diseased hypophysis-diencephalic mechanism. Whether a primary invasion, infection or toxemia affects these organs, thus leading to disturbances in lipoid metabolism and diabetes insipidus, or whether the primary disturbance in lipoid metabolism leads to disease of these neural centers, which in turn causes the diabetes insipidus, is a question that remains to be determined by further investigation.

The exophthalmos occurring in most of the cases is easily explained by the deposition of lipoid masses in the retro-orbital fat. The neurologic signs and symptoms are due to the deposition of the foam cells or to the secondary reactive phenomena in the neural structures.

SUMMARY AND CONCLUSION

A case of xanthomatosis presenting diabetes insipidus, defects in the membranous bones and changes in the nervous system is described. In addition to the deposits of lipoid cells found in most of the organs, the white matter of the central nervous system was the seat of numerous demyelinated plaques filled with compound granular corpuscles and giant glia cells. These two types of cells found in the neural structures are considered analogous to the foam cells and the reactive type of cells (fibrosis and inflammatory cells) demonstrated in other organs. In this disease the hypophysis was the seat of deposits of foam cells, while the tuber cinereum region showed evidences of reactive phenomena (gliosis, fibrosis and inflammatory cells) and occasional compound granular corpuscles and giant glia cells. The process is one of disturbance in lipoid metabolism (cholesterol) and in some respects resembles Gaucher's and Niemann-Pick's diseases, and possibly amaurotic family idiocy.

RÔLE OF THE ANTERIOR ROOTS IN VISCERAL SENSIBILITY

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In the past twenty-five years, the anterior roots have been said by many investigators to contain antidromic fibers which conduct painful impulses from the viscera and skin. The purpose of this experimental study was to determine whether or not there are antidromic fibers in the anterior roots which serve to transmit sensations.

Interest in the presence of sensory fibers in the anterior spinal roots dates from the days of Magendie,[1] Claude Bernard,[2] Walker,[1] Lamarch[1] and Bell.[3] After many experiments, Claude Bernard succeeded in showing that sensation was present in the anterior roots, which he concluded to be due to the presence of recurrent sensory fibers passing from the posterior ganglia up the anterior roots to supply the spinal meninges. His experimental work consisted of laminectomies performed on dogs. It was found that if an anterior root was severed, stimulation of the peripheral stump alone gave rise to a response in the animal and that this result was dependent on the integrity of the dorsal root. It was likewise observed that division of the mixed nerves distal to the junction of the two roots also abolished the sensibility of the anterior root. From this evidence, Claude Bernard concluded that these recurrent sensory fibers crossed from the posterior to the anterior roots, not at their point of union but in the distal plexuses.

In 1911, the validity of the Bell-Magendie law was questioned because of failure to relieve pain by section of the posterior roots. Leonard Kidd[4] proposed that pain could be conducted antidromically over the anterior roots because of the presence of afferent sensory fibers

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1. Quoted by Shaw, R. C.: A Study of Intractable Pain Relative to Rhizotomy and Spinal Section, Brit. J. Surg. **11**:648, 1923.

2. L'oeuvre de Claude Bernard, Paris, J. B. Baillière & Sons, 1881.

3. Bell, Charles: The Nervous System of the Human Body, London, H. Renshaw, 1844.

4. Kidd, Leonard: Afferent Sensory Fibers in the Spinal Ventral Roots, Brit. M. J. **2**:359, 1911.

in these roots. Knapp [5] resected the sixth to the eighth cervical posterior roots for a painful amputation stump, but despite this, pain returned. On the basis of this conception, Kilvington [6] resected the sixth cervical to the first dorsal posterior and anterior roots extradurally for the relief of pain from an amputation neuroma. The pain disappeared permanently.

In 1924, Lehman [7] noted that section of the posterior roots from the fifth to the ninth thoracic in dogs did not destroy visceral sensibility when tension or digital pressure was made on the gallbladder and mesentery, although the abdominal wall was analgesic. He also produced pain by slight compression of the aorta. When he later severed the fifth to the ninth thoracic anterior roots bilaterally in dogs, he found no evidence of pain in the stomach, duodenum, gallbladder and mesenteries when tested as previously described, although the abdominal wall was not analgesic. He performed laparotomies on the latter animals and noticed movements of the extremities and general unrest.

Kodama's [8] experiments supported this conclusion. He severed the fourth thoracic to the second lumbar posterior roots bilaterally and extradurally. When he pressed the liver, gallbladder and branches of the aorta he produced pain. Shaw [1] found that section of the fourth to the seventh lumbar and the first and second sacral posterior roots, with a transverse section of the cord at the second sacral segment, resulted in a retention of deep sensibility in a certain number of animals. He stated that the persistence of pain after the severance of what is held to be the principal afferent path to the central nervous system gives a basis for the supposition that an accessory sensory channel may exist. Nevertheless, he also investigated the effects of sections of the anterior roots in cats on degeneration of the nerve fibers, using the Marchi stain. He found no evidence of afferent sensory fibers possessing a trophic cell outside the cord.

In 1926, Meyer [9] resected the fourth cervical to the second dorsal posterior roots supplying the upper extremities and the eleventh dorsal

5. Knapp, P. C.: Division of the Posterior Spinal Roots for Amputation Neuralgia, Boston M. & S. J. **158**:149, 1908.

6. Kilvington, quoted by Knapp.[5]

7. Lehman, W.: Ueber die sensiblen Fasern der vorderen Wurzeln, Klin. Wchnschr. **3**:1895, 1924.

8. Kodama, Sakugi: A Further Report on the Effect of Stimulation of the Sensory Nerves upon the Rate of Liberation of Epinephrine from the Suprarenal Glands, Zentralbl. f. d. ges. Neurol. u. Psychiat. **39**:255, 1925.

9. Meyer, A. W.: Ueber die fraglichen sensiblen Fasern der vorderen Wurzeln, Deutsche Ztschr. f. Chir. **199**:38, 1926.

to the fifth sacral posterior roots supplying the lower extremities in animals. He found that all sensation, superficial and deep, was destroyed. Meyer concluded that in animals (cats and dogs) sensation is carried entirely in the posterior roots.

Foerster [10] believed that there is a special kind of deep sensibility of the subcutaneous and visceral structures which travels over the anterior roots to a varying degree in individual cases. He has operated in many cases in which both the posterior and the anterior roots were severed and pain remained. He believed that the posterior roots subserve the chief sensory system and that when a sufficient number of roots are severed a sensory defect results. The anterior roots subserve only an auxiliary function in that their isolated interruption never is followed by a sensory defect. The anterior roots, according to Foerster, subserve deep sensibility as well as cutaneous sensibility.

Wartenberg [11] also concluded that a special kind of deep sensibility of the subcutaneous structures travels over the anterior roots to a varying degree in individual cases. After analyzing the material from reported cases he mentioned the following reasons in explanation of the failure of section of the posterior roots to relieve pain: The pathologic process may spread to other roots; pain may originate central to the root section; there may be changes at a distance in the spinal cord; regeneration may occur; there may be changes due to trauma and hemorrhage at the operation; overlap may occur over as many as five segments; at autopsy one may find that not as many roots were severed as were purported to be. It would seem that Wartenberg's conclusion in regard to the anterior roots does not follow from the evidence presented.

More recently, Foerster, Altenburger and Kroll [12] reported an observation which to them seemed to prove the existence of afferent fibers in the anterior roots. In one case the thoracic sympathetic chain was resected from the sixth to the tenth ganglion. During this operation the ninth thoracic nerve was ligated close to its exit from the intervertebral foramen. This produced severe pain. At the same time the adjacent intercostal artery was ligated. At a subsequent operation the seventh to the eleventh dorsal posterior roots were resected. Despite

10. Foerster, O.: Die Leitungsbahnen des Schmerzgefühls und die chirurgische Behandlung der Schmerzzustände, Berlin, Urban & Schwarzenberg, 1927; quoted by Wartenberg: Verhandl. d. Gesellsch. d. deutsch. Nervenartzte **20**:665, 1924.

11. Wartenberg, R.: Klinischen Studien zur Frage der Geltung des Bell-Magendieschen Gesetzes, Ztschr. f. d. ges. Neurol. u. Psychiat. **113**:518, 1928.

12. Foerster, O.; Altenburger, H., and Kroll, F. W.: Ueber die Beziehungen des vegetativen Nervensystem zur Sensibilität, Ztschr. f. d. ges. Neurol. u. Psychiat. **121**:140, 1929.

these procedures the pain continued. The authors believe that in the presence of resection of the sympathetic chain and posterior roots pain could have entered the spinal cord only through the anterior roots.

Davis and Pollock [13] have recently shown that faradic stimulation of the superior cervical sympathetic ganglion did not produce pain after bilateral section of the first twelve posterior spinal roots and the posterior root of the trigeminal nerve. They also sectioned on the right side in man all the posterior roots from the fourth cervical to the fourth thoracic and found loss of all forms of superficial and deep sensation.

Schrager and Ivy [14] showed that dilatation of the cystic duct in the dog, under ethyl carbamate anesthesia, was accompanied by a marked inhibition of respiration, vomiting, struggling and other evidences of pain. They also showed that these responses could be abolished completely by section of the right splanchnic nerve and that they were unaffected by division of the vagi or left splanchnic nerves. Davis, Hart and Crain [15] repeated these experiments and obtained identical results. They found that a complete transverse section of the spinal cord or a lateral lesion which definitely injures the gray matter was necessary to obliterate the responses to these painful impulses. They then sectioned the posterior spinal roots in a series of these animals and found that, if a large enough number were sectioned, painful responses so produced could be abolished. They concluded that visceral afferent impulses are transmitted upward within the spinal cord by short fibers with many relays and synapses which have a juxtagriseal position.

Spiegel [16] and Bernis stimulated the central end of severed splanchnic nerves in animals and found evidence of pain and inhibition of respiration. When both posterior roots or anterolateral columns were severed in animals, faradic stimulation of the cut central stump of the splanchnic nerve revealed no pain or inhibition of respiration. They believed that the pathway for visceral sensibility from stomach and bowel entered the spinal cord by way of the posterior roots, there diffusing with the corresponding somatic nerves.

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13. Davis, Loyal, and Pollock, L. J.: The Peripheral Pathway for Painful Sensations, Arch. Neurol. & Psychiat. **24**:883 (Nov.) 1930.

14. Schrager, V. L., and Ivy, A. C.: Symptoms Produced by Distention of Gallbladder and Biliary Ducts, Surg., Gynec. & Obst. **47**:1, 1928.

15. Davis, Loyal; Hart, J. T., and Crain, R. D.: The Pathway for Visceral Afferent Impulses Within the Spinal Cord, Surg., Gynec. & Obst. **49**:647, 1929.

16. Spiegel, E.: Ueber das Wesen des Bauchschmerzes und seiner Begleiterscheinungen, Wien. med. Wchnschr. **77**:379, 1927.

EXPERIMENTS AND RESULTS

Pain has been produced by faradization of the superior cervical sympathetic ganglion in man by Frazier and Russell,[17] Peet[18] and Foerster[10] and in animals by Davis and Pollock.[19]

All the experimental work was done on cats. Fourteen animals were used and an autopsy was performed in every case to determine the number and kind of roots that had been cut. The experiments may be divided into two groups: In the first, all the cervical and the first two thoracic anterior roots were severed intradurally on the left side, and the superior cervical sympathetic ganglion was stimulated. In five cats the left superior cervical sympathetic ganglion was exposed with the animal under light anesthesia. Faradization of this ganglion in every animal in this group revealed positive evidence of pain as manifested by increased respirations, violent movements of the right forepaw and two hind legs, movement of the head, moaning and wagging of the tail. Postmortem examination revealed in

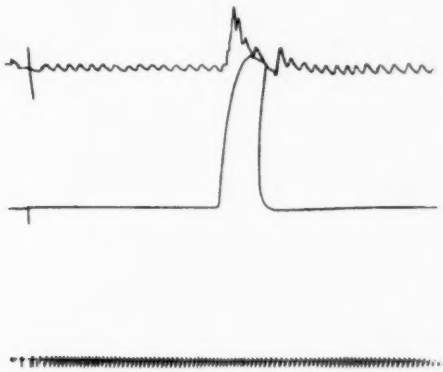

Fig. 1.—Effect of distention of balloon in the gallbladder of a normal cat. Note the elevation of respirations.

every animal severance of all the cervical and the first two thoracic anterior roots on the left side. This indicated the absence of antidromic impulses entering the spinal cord over the gray rami through the anterior roots. When now the first to the ninth posterior roots were severed bilaterally as well, stimulation of the superior cervical sympathetic ganglion still produced pain, which indicated that no afferent fibers alone subserving pain enter the spinal cord through the posterior roots. This is further seen by the fact, reported by Davis and Pollock, that severance of the sympathetic trunk below the superior cervical ganglion, with the

17. Frazier, C. H., and Russell, E. C.: Neuralgia of the Face: An Analysis of 754 Cases with Relation to Pain and Other Sensory Phenomena Before and After Operation, Arch. Neurol. & Psychiat. **11**:557 (May) 1924.

18. Peet, M. M.: Postherpetic Trigeminal Neuralgia; Persistence of Pain After Section of the Sensory Root of the Gasserian Ganglion, J. A. M. A. **92**: 1503 (May 4) 1929.

19. Davis, Loyal, and Pollock, L. J.: The Rôle of the Sympathetic Nervous System in the Production of Pain in the Head, Arch. Neurol. & Psychiat. **27**:282 (Feb.) 1932.

anterior and posterior roots severed, did not prevent the production of such pain. This is in conformity with the anatomic fact that only efferent fibers are present in the cervical sympathetic trunk.

Following is the protocol of one experiment:

CAT 6.—April 16, 1931: All the cervical and the first two thoracic anterior roots were severed on the left side. A complete flaccid paralysis developed in the left forepaw.

April 28: The left superior cervical sympathetic ganglion was exposed and faradized.

Result: Increased respirations, violent movements of three extremities, movement of the head, moaning and wagging of the tail occurred.

The second series of experiments concerned five cats in which all the thoracic and the first lumbar anterior roots were sectioned intradurally on the right side

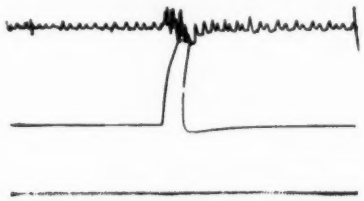

Fig. 2.—Effect of distention of a balloon in the gallbladder of a cat with all the thoracic and first lumbar anterior roots severed on the right side. Note the elevation of respirations.

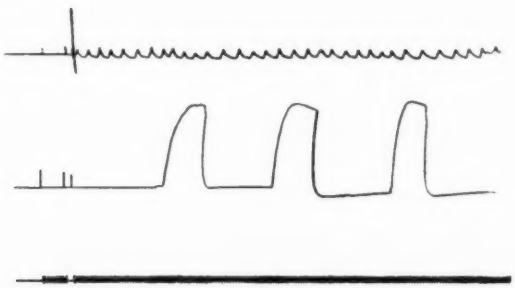

Fig. 3.—Effect of distention of a balloon in the gallbladder of a cat with all the thoracic posterior roots severed on the right side. No elevation of respirations is seen.

(thirteen in all). The gallbladder was then exposed and a balloon inserted into it. The balloon was distended with water at a pressure of 240 mm. of water and resulted in definite evidence of pain. The latter manifested itself by loud crying, violent movements of the head, trunk and all the extremities and an increased depth of respirations. Postmortem examination of each animal revealed thirteen anterior roots severed intradurally and the presence of a balloon in the gallbladder.

Following is a protocol of an experiment which is typical of all:

CAT 13.—May 14, 1931: All the thoracic and the first lumbar anterior roots were severed on the right side.

May 26: The gallbladder was opened and a balloon placed in it.

June 4: The balloon was distended with 35 cc. of water at a pressure of 230 mm. of water.

Result: Loud crying out, increased respirations and violent movement of the head, trunk and all the extremities were noted. Tracings showed inhibition of respirations.

This indicates that if any antidromic impulses travel over the anterior roots, other pathways must likewise exist.

When, however, the posterior roots were sectioned, no pain could be produced, as shown in the following protocol:

CAT 18.—Oct. 22, 1931: Thirteen right posterior roots were severed to include eleven thoracic and two lumbar roots.

November 5: The gallbladder was opened and a balloon placed in it. The entire right side of the chest and abdomen from the axilla to the groin was anesthetic to pinching, pressure and needle prick.

November 12: Thirty cubic centimeters of water was injected into the balloon under a pressure of 230 mm. of water.

Result: There were no signs of pain. The animal is living. Tracings show no inhibition of respirations.

COMMENT

The evidence from the experimental work detailed shows that there are no antidromic fibers for pain in the anterior roots in relation to visceral sensibility. It corroborates the work of Davis and Pollock on the superior cervical sympathetic ganglion with section of the posterior and anterior roots. It further agrees with the published results of Davis, Hart and Crain on section of the posterior roots in relation to abolishing all the responses obtained by forceful dilatation of the gallbladder. Investigators who have previously stated that there must be an antidromic sensory fiber in the anterior roots may have been led to such a conclusion because of the following: First, when the posterior roots were intact, stimulation of the anterior roots produced pain because of nervi nervorum to these roots. Second, when pain persisted after section of the posterior roots, an insufficient number of roots may have been severed. Third, movements due to fright and other causes may have been interpreted as pain. Fourth, when the anterior roots alone were severed, hemorrhage and trauma may have resulted in injury to the posterior roots, or changes may have occurred in the spinal cord at some distance. Fifth, at autopsy one may find not as many roots severed as were purported to be.

It would seem that in such visceral painful impulses as are produced by distention of the gallbladder the anterior roots are in no way a conduction pathway. It is believed, therefore, that the pathway for visceral afferent impulses from the gallbladder passes upward through the right splanchnic nerve through the thoracic sympathetic trunk to the spinal nerves by way of the white rami and then into the spinal cord by way of the posterior roots. Within the cord these impulses pass upward by relays of short spinal paths with synapses in the gray matter.

CONCLUSIONS

1. The anterior roots do not contain antidromic sensory fibers that conduct painful impulses from the viscera, such as that produced by forceful dilatation of the gallbladder.

2. Section of the posterior roots, if a sufficiently large number are severed, will abolish visceral pain produced in a similar manner.

3. The posterior roots, therefore, are the pathways into the spinal cord for certain painful impulses from the viscera.

55 East Washington Street.

INTRACRANIAL HYDRODYNAMICS

II. INFLUENCE OF RAPID DECOMPRESSION OF THE VENTRICULO-SUBARACHNOID SPACES ON THE OCCURRENCE OF EDEMA OF THE BRAIN

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AND
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In the initial article[1] of this series, we described our methods of investigating intracranial hydrodynamics in human cadavers under experimental conditions that rendered certain of our results applicable to the living. Two of our conclusions were:

1. The lateral ventricles and the cisternal and lumbar subarachnoid spaces remained in free communication under all experimental variations in pressure, provided no distortion of the subtentorial structures was artificially produced.

2. In the absence of such distortion there was no evidence of tentorial, medullary or cerebellar movement under any experimental variations in subarachnoid fluid pressure.

Specifically, we could not produce descent of the cerebellum or medulla into the foramen magnum by hydrodynamic means alone, e.g., sudden release of high intracranial fluid pressure through rapid lumbar or cisternal tap. We were therefore unable to confirm the generally accepted importance of the mechanical factor in the etiology of cerebellar "herniation" and bulbar compression in cases in which a block about the foramen magnum had not been artificially effected.

Beyond this our postmortem experiments obviously could not go. It remained, then, to evaluate the other and manifestly vital factors in the causation of the downward displacement of the cerebellar tonsils occasionally found at autopsy in the cases of patients who had been subjected to rapid spinal drainage in the presence of intracranial hypertension. In this respect, it seemed logical to investigate the possible physiopathologic effects of sudden decompression of the ventriculosubarachnoid spaces through rapid drainage of cerebrospinal fluid. A review of the relevant literature revealed:

1. The occurrence of an untoward craniobulbar symptom complex following spinal tap in patients with increased intracranial pressure is

1. Masserman, J. H., and Schaller, W. F.: Intracranial Hydrodynamics: I. Experiments on Human Cadavers, Arch. Neurol. & Psychiat. **29**:1222 (June) 1933.

favored by a too rapid or extensive drainage of cerebrospinal fluid at the time of rachicentesis.[2]

2. Rapid lumbar tap is frequently followed by an increase in blood pressure,[3] a rise of diastolic tension in the retinal artery [4] and other symptoms and signs of increased intracranial pressure.[5]

3. Rapid lumbar tap may cause certain types of hemorrhage into the central nervous system,[6] setting in motion various physiopathologic processes which result in edema of the surrounding nerve tissues.[7]

4. Sudden decompression of cranial hypertension by any other means (surgical procedures, ventricular tap, etc.) is also frequently followed by edema of the brain.[8]

5. In the comparatively rare cases of death attributable directly to lumbar puncture, in which autopsy revealed no apparent cause other than cerebellar "herniation" and medullary compression, a generalized hidrosis of the brain has been a frequent concurrent observation.[9]

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2. (*a*) Bing, R.: Compendium of Regional Diagnosis in Affections of the Brain and Spinal Cord, New York, Rebman Company, 1913. (*b*) Cushing, H.: Tumors of the Nervus Acusticus, Philadelphia, W. B. Saunders Company, 1917. (*c*) Lobingier, A. S.: Colorado Med. **16**:303, 1918. (*d*) Ayer, J. B.: Puncture of the Cisterna Magna, Arch. Neurol. & Psychiat. **4**:529 (Nov.) 1920. (*e*) Crothers, B.: Surg., Gynec. & Obst. **37**:790 (Dec.) 1923. (*f*) Pappenheim, M.: Lumbar Puncture, London, John Bale Sons & Danielsson, Ltd., 1925, p. 26. (*g*) Constantin, L.: Internat. Clin. **4**:17 (Dec.) 1926. (*h*) Ayer, J. B., in Dana, C. L., et al.: The Human Cerebrospinal Fluid, Association for Research in Nervous and Mental Diseases, New York, Paul B. Hoeber, Inc., 1926, vol. 4, 170.

3. (*a*) Kahler, H.: Wien. klin. Wchnschr. **33**:1007 (Nov. 11) 1920. Blood pressure is considered by (*b*) Ayer (footnote 2*h*, p. 159) and (*c*) Block and Oppenheimer (Comparative Study of Intraspinal Pressure, Blood Pressure and Intra-Ocular Tension, Arch. Neurol. & Psychiat. **11**:444 [April] 1924) roughly to follow cerebrospinal fluid pressure.

4. Berens, C.; Smith, H. T., and Cornwall, L. H.: Changes in the Fundus and in the Blood Pressure in the Retinal Arteries in Increased Intraspinal Pressure, Arch. Neurol & Psychiat. **20**:1151 (Dec.) 1928. Retinal artery tension is considered by Bailliart, Magniel and Saragea (Arch. d. mal. du cœur **17**:289, 1924) to parallel intracranial pressure.

5. (*a*) Rawlings, L. B.: West. M. News **10**:145, 1918. (*b*) Grant, F. S., in Dana et al. (footnote 2*h*, p. 227). (*c*) Schönbeck, O.: Die Gefahren der Lumbalpunktion, Arch. f. klin. Chir. **117**:309, 1915-1916.

6. (*a*) Ossipow: Deutsche Ztschr. f. Nervenh. **9**:350, 1912. (*b*) Ponfick, quoted by Pappenheim.[2f] Constantin.[2g] Schönbeck.[5c]

7. (*a*) Hill, Leonard: Physiology and Pathology of the Cerebral Circulation, London, J. & A. Churchill, 1896. (*b*) Cannon, W. B.: Am. J. Physiol. **6**:91, 1901. (*c*) Phelps: Traumatic Injuries of the Brain and Its Membranes, New York, D. Appleton and Company, 1897. (*d*) Landis, E. M.: Am. J. Physiol. **83**:528, 1928.

8. (*a*) Kraus, F.: Surgery of the Brain and Spinal Cord, translated by H. A. Haubold, New York, Rebman Company, vol. 1, p. 196. (*b*) Grant.[5b]

9. (*a*) Chiari: Denkschriften Akademie der Wissenschaften, Wien **63**:71, 1895. (*b*) Constantin.[2g] Schönbeck.[5c]

To sum up: A consideration of the literature points to the possibility that rapid removal of cerebrospinal fluid by lumbar tap in cases of intracranial hypertension may cause a secondary and greater increase in intracranial pressure, and possibly also edema of the central nervous system.

In the light of these data, the following question naturally arose: In cases in which the hindbrain is not initially displaced into the foramen magnum by distortion of the cranial contents,[10] might not postrachicentetic "herniation" be due to swelling of the brain produced by the sudden lowering of the tension of the cerebrospinal fluid? It seemed entirely conceivable that a relatively small increase in the size of the cerebellum, in view of the rigid space limitations of the subtentorial chamber,[11] could not only cause symptoms of bulbar compression [12] but also result in obliteration of the basal cistern and extrusion of the cerebellar tonsils into the foramen magnum, the latter being the only opening into which the hindbrain could easily expand. Various degrees of cerebellar and medullary edema, conceivably, could also cause corresponding degrees of compression and ischemia of the vital medullary centers,[13] and thus give rise to the various symptoms of "bulbar shock" [14] that occasionally follow rapid spinal drainage. Moreover, the occurrence of postrachicentetic cerebrobulbar edema could, *a priori,* explain such other empirically well recognized clinical phenomena as: (1) the advisability of very gradual decompression in cases of increased intracranial cerebrospinal fluid pressure; [15] (2) the frequently prolonged period of latency of the untoward postpuncture symptom complex,[16] and the significant similarity of the latter to the syndrome characteristic

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10. Ophüls, W.: Virchows Arch. f. path. Anat. **151**:53, 1898. Meyer, A.: Herniation of the Brain, Arch. Neurol. & Psychiat. **4**:387 (Oct.) 1920. Schaller, W. F.: Mechanism of Compression in a Case of Tumor of the Cerebellopontile Angle, Arch. Neurol. & Psychiat. **17**: 609 (May) 1927. Cushing.[2b] Chiari.[9a]

11. Dandy, W. E.: Bull. Johns Hopkins Hosp. **34**:245 (Aug.) 1923. Crothers.[2e] Hill.[7a] Kraus.[8a]

12. Heimlich, F.: Arch. f. Psychiat. **93**:241, 1931.

13. Trotter, Wilfred: Brit. J. Surg. **2**:520, 1915. Heimlich.[12]

14. Martin, E.: Lyon méd. **139**:162, 1898. Minet: J. de méd. de Paris **16**:132, 1914. La Voix: Death Following Lumbar Puncture, Thèse de Lille, 1909. Stadelman, E.: Berl. klin. Wchnschr. **32**:581, 1895. Tuffier: Bull. et mém. Soc. d. Chirurgiens de Paris **31**:1119 (Nov. 8) 1905.

15. (*a*) Quincke: Therapeutic Indications for Lumbar Puncture, Therap. Monatsh. **28**:469, 1914. (*b*) Tromner, E.: Zentralbl f. d. ges. Neurol. u. Psychiat. **31**:423, 1923. Pappenheim.[2f] Constantin.[2g] Ayer.[2h] Grant.[5b]

16. Keegan, J. J.: Nebraska M. J. **15**:97 (March) 1930. Helot, T. J.: M. J. & Rec. **129**:136 (Feb. 6) 1929. Constantin.[2g] Schönbeck.[5c] Quincke.[15a]

of edema of the brain,[17] and (3) the delayed onset of the majority of postpuncture deaths.[18]

Further summary of the vast literature on these subjects will be reserved for the third article of this series. The remainder of the present report will be devoted to a description of certain experiments designed to permit direct investigation of the relationship of rapid decompression of intracranial hypertension to the subsequent occurrence of edema of the brain in dogs.

PROCEDURE

Pairs of large dogs were simultaneously anesthetized with morphine sulphate and a brand of chlorbutanol, these anesthetics being chosen for their relatively constant effect on intracranial pressures as compared with the varying effects of ether.[19] A needle was then inserted into the cisterna basalis of one animal, designated dog A, and connected to a reservoir of modified Ringer's solution.[20] This arrangement, of course, rendered it possible to maintain in the subarachnoid system of dog A a tension corresponding to the height of the fluid in the reservoir above the level of the dog's head.

In our earlier experiments, the other of the pair of animals, designated dog B, was prepared according to a technic described for cadavers in our previous article.[21] Ventricular, cisternal and lumbar punctures were done, and each needle was connected to a water manometer.[22] In addition, the ventricular needle was made to communicate through a Y-tube with a pressure bottle containing sterile Ringer's solution. With this arrangement we could then produce any desired initial intraventricular tension and observe its transmission to the subarachnoid system of dog B. Further, we could reduce the subarachnoid tension directly by either cisternal or lumbar tap and again note the corresponding pressure variations in the other two loci punctured.

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17. Quincke: Lumbar Puncture, Deutsche Klin. **6**:1, 1906. Reichman: Ztschr. f. d. ges. Neurol. u. Psychiat. **11**:581, 1912. The relationship between postpuncture symptoms and the occurrence of edema of the brain will be developed further in a later paper.

18. Constantin.[2g] Schönbeck.[5c]

19. Cappelletti, G.: Arch. ital. de biol. **25**:463, 1900. Myerson, A., and Loman, J.: Internal Jugular Venous Pressure in Man, Arch. Neurol. & Psychiat. **27**:836 (April) 1932.

20. Formula given by Weed, L. H., and Wegeforth, P.: J. Pharmacol. & Exper. Therap. **13**:317, 1919.

21. Figure 1 of the article referred to in footnote 1 illustrates the general arrangement of the preparation of dog B, except that a pressure bottle was substituted for the movable reservoir, and the jugular injection system was omitted.

22. Triple puncture was facilitated by selecting large dogs and by maintaining the animal in extreme spinal flexion. Patency of each of the needles was indicated by the occurrence of variations in pulse and respiratory pressure in the corresponding manometers. These rhythmic fluid excursions were most marked in the cisternal manometer, less in the ventricular and least in the lumbar.

This experimental arrangement was based on our experience with multiple puncture in human beings. We soon found, however, that a dog's ventriculosubarachnoid system seemed to differ from that of man [23] in not being able rapidly to transmit changes in pressure from one portion to another. Thus, if we suddenly raised a dog's ventricular pressure to 75 cm. of water, the cisternal and lumbar pressures would climb to this level only after a variable interval. Conversely, if a rapid lumbar tap was then done, the curves of intraventricular and intracisternal tension would show a lag of from one to seven seconds before beginning a decline parallel to that of the pressure in the lumbar sac.[24]

In view of these facts we soon abandoned triple puncture, as our experiments were intended primarily to determine the effects of rapid decompression through sudden drainage of subarachnoid fluid on the incidence of edema of the brain. Our later preparations of dog B were therefore simplified to the insertion of a single cisternal needle, which was then connected directly to a pressure bottle half filled with sterile Ringer's solution and equipped with a water manometer. Pressures in the dog's subarachnoid system could thus be varied (discounting the momentary lags mentioned) directly as those in the pressure bottle, and corresponded to the manometric readings of the latter.

The usual experiment consisted in synchronously raising the ventriculosubarachnoid pressures of both dogs to 75 cm. of water throughout a period of from thirty to sixty minutes. The pressure of dog A was then kept constantly at this level for four hours, whereas the cisternal pressure of dog B was suddenly reduced to 5 cm. of water at the expiration of the first half hour of the artificial intracranial hypertension. At the end of the four hour period, both brains were removed and sections taken from each for microscopic study. The ventricles were then opened widely, and all excess fluid was drained away or removed with blotting paper from the exposed peripheral and ventricular surfaces. Following this, both brains were carefully weighed and placed in a drying oven for twenty-four hours. The brains were then weighed again to determine the percentage of water lost.

RESULTS

The results may be summarized as follows: A series of eight brains from control dogs anesthetized as described showed an average loss in

23. Dandy, W. E., and Blackfan, K. D.: An Experimental and Clinical Study of Internal Hydrocephalus, J. A. M. A. **61**:2216 (Dec. 20) 1913; Internal Hydrocephalus, Am. J. Dis. Child. **8**:406 (Dec.) 1914. Cushing, H.: Studies in Intracranial Physiology and Surgery, New York, Oxford University Press, 1925. Fremont-Smith, F., and Hodgson, J. S., in Dana, C. L. et. al.,[2h] p. 172. Ayer, J. B.: Spinal Subarachnoid Block as Determined by Combined Cistern and Lumbar Puncture, Arch. Neurol. & Psychiat. **7**:38 (Jan.) 1922. Ayer.[2d] Ayer,[2h] p. 159. Ruggles, A. H.: Observations in Ventricle and Cistern Puncture, Arch. Neurol. & Psychiat. **11**:227 (Feb.) 1924. Dahlstrom, S., and Wilderae, S.: Ztschr. f. d. ges. Neurol. u. Psychiat. **22**:75, 1921. Solomon, H. C.; Thompson, L. J., and Pfeiffer, H. M.: Circulation of Phenolsulphonephthalein in the Cerebrospinal System, J. A. M. A. **79**:1014 (Sept. 23) 1922.

24. The lag of intraventricular pressures during lumbar drainage was present on the first trial. At the end of an experiment, however, the lag was even more pronounced, indicating partial edematous closure of the aqueductus cerebri or subarachnoid block at the foramen magnum. Similar observations have been recorded by Eyster.[29]

weight of 71.9 per cent (range, from 68.8 to 73.5 per cent) after desiccation. Eight A brains (subjected to a constant ventriculosubarachnoid pressure of 75 cm. of water) lost 74.1 per cent (range, from 70.8 to 76.3 per cent) of their weight on drying, whereas the corresponding series of B brains showed an average loss in weight of 78.2 per cent (range, from 72.1 to 82 per cent)—a difference in water content definitely in favor of the brains subjected to sudden fluid decompression.

Dr. James E. Davis,[25] in commenting on the corresponding series of sections submitted to him for diagnosis, wrote:

> Eight sections labeled dog A were studied.
>
> Eight sections labeled dog B were studied.
>
> Comparing the two sets without knowing which was the control set, a general statement can be made that sections marked dog B show a slightly greater degree of edema and nuclear pyknosis.
>
> There are, however, certain slides in the A group that show fairly definite edema, but the A group tissue, as a rule, has greater compactness and an essentially normal nuclear pigment content.

COMMENT

The difference in the average water content of the brains of the A and B series cannot be explained on the grounds of an increased blood content of the B brains subjected to reduced pressure during the latter part of the experiment, because the possible difference in blood volume is small,[26] and because this difference would be even further minimized by the greater specific gravity of the blood in comparison with that of the tissue fluids which it replaced. Again, if edema of the brain varied directly as the ventriculosubarachnoid fluid pressure, the brains of series A should have shown the greater loss of fluid. The increased water content of our B series must therefore have been due primarily to a comparatively greater intracellular or pericellular edema consequent on the rapid decompression with drainage of the subarachnoid fluid.[27]

Reports of analogous experiments in the available literature seem limited to the following: In 1892, Dean [28] found that "brain areas, from which some little time previously a local compressing agent had been removed, contained three per cent more water than normal brain areas." Eyster [29] found that after the intracranial pressure of a dog had been experimentally varied for some time, its brain became edemat-

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25. Davis, J. E.: Personal communication to the authors from the Department of Pathology, Detroit College of Medicine and Surgery.

26. Weil, A.; Zeiss, F. R., and Cleveland, D. A.: Am. J. Physiol. **98**:363 (Oct.) 1931. Hill (footnote *7a*, p. 77).

27. The conditions of the experiment do not permit any exact conclusions to be drawn from a comparison of the fluid contents of normal and experimental brains.

28. Dean, quoted by Hill.[7a]

29. Eyster, J. A. E.: J. Exper. Med. **8**:565, 1906.

ous. This author also made the interesting observation that when edema of the brain had become established more or less blocking occurred at the isthmus tentorii cerebelli or in the craniovertebral junction, after which the hindbrain, confined elsewhere, crowded its way into the spinal canal and thus compressed the medulla. Ossipow [6a] and Maystre [30] found that hyperemia and hemorrhages of the brain followed lumbar puncture in dogs. Since Hill,[7a] Cannon [7b] and others directly relate hemorrhage of the brain to edema of the brain, these reports support the contention that rapid decompression by drainage of fluid may be a frequent cause of cerebral hidrosis.

Our own series of experiments is admittedly too small to permit any precise conclusions. The indications, however, are that a sudden reduction of high intracranial pressure may be just as capable of causing cerebral shock and edema as a sudden disturbance of intracranial fluid equilibrium produced in any other manner.[31]

SUMMARY

The possibility that rapid decompression of intracranial hypertension may cause cerebral cellular damage and edema is presented. This concept, if clinically applicable,[32] may well explain such heretofore empiric tenets as: (1) the necessity of gradual decompression when cerebrospinal fluid is withdrawn by rachicentesis in cases of cranial hypertension; (2) the occurrence of postpuncture cerebral or bulbar symptoms if this precaution is neglected, and (3) the advisability of evenly maintaining the ventriculosubarachnoid pressure during the intrathecal or intraventricular injection of air for roentgenographic purposes.[33]

A more complete review of the literature, with a presentation of original experimental and clinical evidence relative to the further development of this subject, will appear in a subsequent article of this series.

30. Maystre: The Dangers of Lumbar Punctures, Thèse de Montpellier, 1903.

31. Trotter, W.: Brit. J. Surg. **2**:520, 1915. Sargent, P., and Holmes, G.: J. Roy. Army M. Corps **27**:300 (Sept.) 1916. Lobingier.[2c] Grant, in Dana et al.[2b] Cannon.[7b] Kraus.[8a]

32. Evidence that the theoretical and experimental considerations outlined in this contribution are applicable to man will be presented in a later paper.

33. Grant, F. C.: Ventriculography and Encephalography, Arch. Neurol. & Psychiat. **27**:1310 (June) 1932. Tromner, E.: Zentralbl. f. d. ges. Neurol u. Psychiat. **31**:423, 1923. Martin and Uhler: Am. J. Roentgenol. **9**:543, 1922. Bengel: Deutsche Ztschr. f. Nervenh. **25**:230, 1922. Denk: München. med. Wchnschr. **69**:799, 1922. Almens and Hirsch: München. med. Wchnschr. **70**:41, 1923. Cestan and Riser: Bull. et mém. Soc. d. hôp. de Paris **48**:953, 1924. Sommer, F. C.: A New Apparatus for Replacement of Cerebrospinal Fluid by Air in Encephalography and Ventriculography, Arch. Neurol. & Psychiat. **26**:1337 (Dec.) 1931. Masserman, J. H.: Simplified Encephalography Technique, Calif. & West. Med. **37**:249 (Oct.) 1932.

HALOGEN BALANCE OF BLOOD, SPINAL FLUID AND URINE

IN PATIENTS WITH CONVULSIVE STATES ON BROMIDE-CHLORIDE THERAPY

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The objective in the analytic studies herein reported was to ascertain whether chlorine was displaced from the blood into other body fluids or eliminated in the urine to compensate for the accumulation of the bromine in the blood and any other body fluids following the ingestion of bromide by mouth. Comparative analyses for chlorine and bromine were made in the blood, spinal fluid and urine of a group of sixteen female epileptic subjects who had received chloride-bromine treatment for one year or more and all of whom exhibited a satisfactory physiologic response to the therapy. Details of the relative quantities of bromide and chloride fed to the epileptic patients have been presented by one of us (Dr. Notkin [1]) in an earlier publication. There also was described the method adopted for the analyses reported in this communication.

TECHNIC

Twenty milliliters of blood, 100 ml. of urine and the maximum quantities of spinal fluid available (from 8 to 20 ml.) were used in the analyses and were incinerated slowly (for from two to three days) over a free flame. Control experiments for recovery of chlorine and bromine with this analytic method after the addition of the pure salts gave yields of approximately 95 per cent.

Specimens of spinal fluid were drawn immediately after venipuncture in the morning under basal conditions. An attempt was made to collect all urine voided during the twenty-four hours immediately preceding the drawing of blood, but the lack of intelligent cooperation on the part of the patients introduced some uncertainty concerning the accuracy of the total volumes for the twenty-four hour period. However, an accurate estimate of the twenty-four hour volume of urine was not essential, since the purpose of the urinalysis was to determine the ratio of bromine to chlorine rather than the total amount of either halogen excreted.

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1. Notkin, J.: Chloride-Bromide Treatment in Epilepsy, Arch. Neurol. & Psychiat. **21**:165 (Jan.) 1929.

Although the specimens of urine received for analyses may not have been the total amount excreted per day, the analysis of these samples for comparative concentrations of bromine and chlorine has afforded more instructive information than analyses of casual specimens for any short period of the day.

RESULTS

The distribution of chlorine between plasma and cells was studied in a group of nine patients who had been receiving sodium chloride and sodium bromide in proportions of 1 : 10 for a period of one year or longer. The daily intake varied from 2.2 to 4.4 Gm. of sodium bromide and one tenth of this amount of sodium chloride. For cell chlorine, Wu [2] gave an average figure of 52.9 milli-equivalents per liter. Although the nine subjects in table 1 present figures for cell chlorine varying in either direction from Wu's average figure, in all cases the

TABLE 1.—*Halogen Balance of Plasma and Blood Cells During Bromide Therapy* *

Subject	Plasma			Blood Cells			C.Br. / P.Br.	C.Cl. / P.Cl.
	Br.†	Cl.†	Total	Br.	Cl.	Total		
E. R.	41.9	69.1	111.0	28.0	44.4	72.4	0.66	0.64
C. A.	20.3	96.0	116.3	12.8	58.2	71.0	0.63	0.60
M. L.	29.0	79.4	108.4	17.8	42.8	60.6	0.61	0.54
L. H.	26.1	85.3	111.4	15.3	53.6	68.9	0.58	0.62
M. R.	18.1	82.0	100.1	11.8	55.8	67.6	0.65	0.68
A. B.	30.1	78.6	108.7	18.6	48.9	67.5	0.61	0.62
E. B.	10.6	95.0	105.6	7.1	54.4	61.5	0.67	0.57
R. P.	19.7	90.7	110.4	10.8	59.0	69.8	0.55	0.65
I. S.	24.6	79.7	104.3	12.0	48.9	60.9	0.49	0.61
Average							0.605 ±0.04	0.614 ±0.03

* In this and the succeeding tables, all of the results are expressed in terms of milli-equivalents per liter.

† In the tables Br. = bromine; Cl. = chlorine.

concentration of total halogens far exceeds 52.9 milli-equivalent per liter, the increases ranging from 15 to 36 per cent. Approximately one hour elapsed between the time of drawing the blood and the time of separating the blood cells by centrifugation. During this period the specimens were not shielded from contact with air by a protecting layer of mineral oil. Van Slyke, Wu and McLean,[3] Fredericia [4] and Myers and Short [5] have directed attention to the increases of plasma or serum chlorides effected by the transfer of chlorides from the blood cells to the plasma consequent to the loss of carbon dioxide from the plasma on standing. McLean [6] stated that this exchange of chloride takes place

2. Wu, H.: J. Biol. Chem. **51**:21, 1922.

3. Van Slyke, D. D.; Wu, H., and McLean, F. C.: J. Biol. Chem. **66**:765, 1925.

4. Fredericia, L. S.: J. Biol. Chem. **42**:245, 1920.

5. Myers, V. C., and Short, J. J.: J. Biol. Chem. **44**:47, 1920.

6. McLean, F. C.: J. Exper. Med. **22**:366, 1915.

slowly, and that it is necessary to separate the cells by centrifugation within from two to three hours to avoid this increase in plasma chlorides. Since any error introduced through this transfer of halides from cells to plasma during standing of the blood for one hour in contact with air would decrease the concentration in the cells, it is apparent that the abnormally high figures for total halogens of the blood cells after bromide-chloride therapy possess real significance.

McLean placed the chlorine concentration of normal blood plasma between 97 and 105 milli-equivalents per liter. All of the subjects in table 1 exhibit a decrease in chlorine concentration of plasma below the normal level, varying between 69 and 96 milli-equivalents per liter. Seven of the nine subjects present figures for total halogens above the

TABLE 2.—*Relative Concentrations of Halogens in Blood, Spinal Fluid and Urine*

	Blood				Spinal Fluid				Urine			
Name	Br.	Cl.	Total	Br./Cl.	Br.	Cl.	Total	Br./Cl.	Br.	Cl.	Total	Br./Cl.
L. H.	17.0	67.3	84.3	0.25	14.2	104.1	118.3	0.14	23.5	91.5	115.0	0.26
R. W.	16.7	69.9	86.6	0.24	11.4	107.5	118.9	0.11	6.31	36.2	42.5	0.17
A. W.	25.2	55.0	80.2	0.46	18.6	102.8	121.4	0.18	5.53	36.0	41.5	0.15
C. G.	26.2	55.0	81.2	0.48	21.7	98.5	120.2	0.22	23.9	66.0	89.9	0.36
D. S.	9.7	70.1	79.8	0.14	7.09	118.0	125.1	0.06	10.3	89.8	100.1	0.11
M. D.	18.6	67.9	86.5	0.27	13.8	109.0	122.8	0.13	26.6	108.0	134.6	0.25
M. R.	15.2	67.2	82.4	0.23	12.2	112.0	124.2	0.11	10.7	51.8	62.5	0.21
M. L.	18.8	67.5	86.3	0.28	11.7	113.0	124.7	0.10	32.5	142.0	174.5	0.23
E. B.	20.0	62.6	82.6	0.32	15.4	107.0	122.4	0.14	52.2	205.0	257.2	0.25
M. B.	19.6	68.0	87.6	0.29	15.7	106.0	121.7	0.15	19.6	85.3	104.9	0.23
R. P.	14.7	70.2	84.9	0.21	11.5	113.0	124.5	0.10	27.3	157.0	184.3	0.17
I. S.	18.2	62.2	80.4	0.29	13.1	110.0	123.1	0.11	5.3	24.6	29.9	0.22
H. H.	18.2	65.0	83.2	0.28	12.8	112.0	124.8	0.11	30.9	124.0	154.9	0.21
J. M.	16.0	55.2	71.2	0.29	15.3	110.0	125.3	0.14	16.8	75.8	92.4	0.22
F. H.	22.0	52.4	74.4	0.42	21.3	110.0	131.3	0.19	17.9	87.0	104.9	0.21
H. D.	32.5	49.2	81.7	0.66	32.3	87.0	119.3	0.37	16.6	28.3	44.9	0.59

upper normal level for chlorine in plasma, and the remaining two figures lie within the normal limits. The range of deviation of the total plasma halogens from the upper normal level for chloride was from -5 to $+11$ per cent. Since the experimental error in the analytic method may be $\pm$ 10 per cent, the observed variations of total halogens from the upper normal level of plasma chlorine has no significance. From the data reported by Myers and Short it is evident that during standing unprotected by oil for periods varying from two to twenty-four hours the rise in plasma chlorides varied from 2 to 10 per cent. If we concede an increase of 10 per cent in plasma halogens due to this transfer from cells to plasma, the correction thus introduced would bring our results more nearly within the normal range.

The fact that the analyses of plasma halogens gave normal values and those of cell halogens gave high values, while whole blood halogens were within normal limits (table 2), indicates that the proportion of cells to plasma was low. This was not checked by hematocrit readings

or erythrocyte counts, but our general experience with this type of patient has shown a prevalence of anemia of varying degree.

Both the ratio of chlorine in cells to chlorine in plasma $\left(\frac{\text{C.Cl.}}{\text{P.Cl.}}\right)$ and the ratio of bromine in cells to bromine in plasma $\left(\frac{\text{C.Br.}}{\text{P.Br.}}\right)$ have been calculated and reported. The average ratio for chlorine is 0.614 ± 0.03, and that for bromine, 0.605 ± 0.04. McLean stated that the chlorine of blood cells approximates one half of the plasma chlorine. Wu has determined plasma and cell chlorine, and his results for the ratio from twenty analyses varied from 0.43 to 0.53, averaging 0.50. Our ratios for both bromine and chlorine are approximately 20 per cent above Wu's and McLean's averages for the relative concentrations of chlorine in cells and plasma of normal blood. Moreover, the difference between the chlorine and bromine ratios is less than the average deviations of the figures for bromine or for chlorine from their corresponding means.

Hastings and van Dyke [7] reported high ratios of bromine (cells) : bromine (serum), in some instances reaching 2.0, with ratios of chlorine (cells) : chlorine (serum) of 0.5 after the feeding of massive doses of sodium bromide to dogs. Although in table 1 wide variations were noted among the concentrations of bromine in plasma and blood cells for any particular specimen, the distribution was fairly constant and analogous to the distribution of chlorine. In other words, bromine penetrates the blood cells just as readily as chlorine does.

Bernouilli,[8] Ulrich [9] and von Wyss [10] stated that following bromide therapy bromide is substituted for chloride in equal proportions in blood plasma. From the data of table 1, as well as from those reported by the authors quoted, one cannot determine whether the effect of bromides on blood plasma is limited to substitution. That chlorine is displaced from plasma into the cells appears to be indicated by the low plasma chlorine and the high cell-plasma ratio. However, it is possible that an addition of bromides to chlorides may also have resulted from the therapy, since the concentrations of total halogens in both cells and plasma are at or above the maximum normal level for chlorine.

One objective in this investigation was to determine whether chlorine was displaced from blood into other body fluids. The results from the sixteen cases utilized for this study are reported in table 2. Normal whole blood contains from 76 to 88 milli-equivalents of chlorine per liter. All the cases in this group show low chlorine concentrations, although the total halogens were within the normal range for blood chlorides. Normal spinal fluid has an average concentration of 125

7. Hastings, A. B., and van Dyke, H. B.: J. Biol. Chem. **92**:27, 1931.

8. Bernouilli, E.: Arch. f. exper. Path. u. Pharmakol. **73**:355, 1913.

9. Ulrich, A.: Cor.-Bl. f. schweiz. Aertze **44**:641, 1914; Schweiz. Arch. f. Neurol. u. Psychiat. **13**:622, 1923; M. J. & Rec. **126**:41, 1927.

10. von Wyss, H.: Deutsche med. Wchnschr. **39**:345, 1913.

milli-equivalents per liter. All of the subjects in table 2 gave concentrations lower than this, averaging 107.5 milli-equivalents. The total halogens, however, range from 118.3 to 131.3, giving an average of 123. There was, then, no displacement of chlorine into spinal fluid, but rather a substitution of spinal fluid chlorine by bromine.

Wuth [11] stated that in the bromide therapy for epilepsy it is unwise to permit the bromide concentration of blood to exceed 125 mg., as sodium bromide per hundred milliliters, or 12.1 milli-equivalents of bromine per liter of blood serum. Eight of the nine cases in table 1 show bromine concentrations of plasma exceeding the limit proposed by Wuth for serum. In table 2, fifteen of the sixteen patients present figures for bromine in whole blood above 12.1 milli-equivalents per liter. Bernouilli has emphasized the necessity of maintaining in blood a low bromide-chloride ratio (0.25), or, as he calls it, a low relative bromide content, in order to obtain maximum therapeutic effect and to avoid bromide intoxication. In table 2, the ratios bromine-chlorine of whole blood vary from 0.14 to 0.66, and ten subjects show ratios above 0.25. All of these patients manifested a satisfactory physiologic response to bromide therapy without any evidence of toxic reactions. These observations corroborate the conclusion previously stated that no level of bromide concentration in blood is optimal for all epileptic patients. The individual requirements of each subject must be determined empirically by an experienced observer.

From an inspection of the ratios (table 2) for blood and urine in the individual cases, it will be seen that in all, except L. H., the ratio for urine is lower than that for blood. The variations of the urine ratios from those for blood are between extremes + 4 and — 67 per cent of the blood ratios. For the entire series, the urine ratios show an average of 77 per cent of the blood ratios. Hence, in general, chlorine forms a larger fraction of the total halogens of the urine than that found in blood for fifteen of the sixteen subjects studied. These results suggest a greater loss of chlorine than of bromine in the urine under bromide-chloride therapy.

Since the development of toxic symptoms during bromide therapy must depend on the amount of bromide retained and its distribution within the body and not on the quantity excreted in the urine, ratios for bromine-chlorine in spinal fluid were calculated for the sixteen subjects in table 2 as indexes of distribution of the retained bromide among body fluids. Ratios for spinal fluid in all cases are less than the corresponding ratios for whole blood, ranging from 26 to 56 per cent, the average being 46 per cent of that of the whole blood ratios. Since comparisons in the table show greater bromine concentrations, it seemed possible that the distribution of bromine between blood plasma

11. Wuth, Otto: Rational Bromide Therapy: New Methods for Its Control, J. A. M. A. **88**:2013 (June 25) 1927.

and spinal fluid might vary definitely from that for chlorine. With the object of studying the penetration of bromine into spinal fluid, in table 3 comparisons have been made of bromine concentrations in blood plasma and in spinal fluid in six subjects. In these cases, the ratio of spinal fluid bromine-plasma bromine varies from 0.40 to 0.67, with an average of 0.53. Hence, the bromine concentration in spinal fluid in these subjects is not in equilibrium with the bromine concentration in blood plasma. These data for bromine form a definite contrast to the distribution of chlorine between the two fluids and also to the distribution of both bromine and chlorine between plasma and blood cells (table 1). Although the paucity of data in table 3 prohibits deduction of general conclusions, there is evident the suggestion that either a part of the bromine is in a nondiffusible form in blood plasma, or the separating membranes between spinal fluid and blood are less permeable to bromine than to chlorine.

TABLE 3.—*Distribution of Bromine Between Blood Plasma and Spinal Fluid*

Name	Blood Plasma	Spinal Fluid	Spinal Fluid Bromine / Blood Plasma Bromine
L. H.	26.1	14.2	0.54
M. R.	18.1	12.2	0.67
M. L.	29.0	11.7	0.40
E. B.	32.0	15.4	0.48
R. P.	19.7	11.5	0.58
I. S.	24.6	13.1	0.50
Average			0.53

The fact that the relative concentrations of bromine and chlorine in urine, as determined by the ratio of bromine-chlorine, vary over a wide range from those for blood and even more definitely from those for spinal fluid, raises some doubt concerning the value of utilizing quantitative analyses of urine for chlorine and bromine as indexes either of the therapeutic dose or of the toxic effects of bromides. If, however, analytic figures for urine ratios of bromine-chlorine are to be interpreted in terms of bromine retained in the blood, it is essential to recognize that the urine ratio is in general from 20 to 25 per cent below that for whole blood.

With the object of determining the rate of retention of bromide in body fluids following the inception of bromide therapy, specimens of whole blood, spinal fluid and of urine were analyzed for chlorine and bromine, twenty-four, seventy-two and one hundred and forty-four hours after the beginning of bromide therapy with 1.1 Gm. of sodium bromide per day. These fluids were collected for analysis exactly as described for the foregoing experiments. Table 4 reveals that at the end of twenty-four hours after the initial dose of bromide, bromine is found in measurable quantities in blood, spinal fluid and urine. Subjects A. S. and S. G. show a fall in blood chlorine as the concentration of

bromine rises, but in N. de S., a significant rise in chlorine accompanies the slight increase in bromine. Figures for chlorine and total halogens of spinal fluid do not vary outside a reasonable experimental error of ± 10 per cent. Hence, these variations are insignificant. As noted in analytic studies already described, the ratios for bromine-chlorine in urine are less than the corresponding ratios for whole blood, and in the majority of cases are also less than the ratios for spinal fluid. The

TABLE 4.—*Halogen Balance of Blood, Spinal Fluid and Urine for the First Six Days of Bromide Therapy*

		Spinal Fluid				Blood				Urine			
Name	Hours	Br.	Cl.	Total	Br./Cl.	Br.	Cl.	Total	Br./Cl.	Br.	Cl.	Total	Br./Cl.
N. de S.	24	3.4	112	115.4	0.030	4.4	68.0	72.4	0.064	9.4	177.0	186.4	0.053
	72	5.3	114	119.3	0.046					6.8	126.0	132.8	0.057
	144	5.5	117	122.5	0.047	6.2	78.8	85.0	0.078	3.4	14.0	17.4	0.250
A. S.	24	5.8	113	118.8	0.051	3.7	74.0	77.7	0.050	0.77	36.0	36.77	0.021
	72	6.5	122	128.5	0.053	6.5	62.6	79.1	0.104	2.6	25.6	28.2	0.101
	144	6.8	115	121.8	0.059	...	....	....	.....	8.7	98.0	106.7	0.088
S. G.	24	4.8	117	121.8	0.041	3.0	68.0	71.0	0.044	3.3	93.0	96.3	0.035
	72	8.2	94	102.2	0.087	5.7	68.0	73.7	0.083	7.4	138.0	145.4	0.053
	144	8.0	102	110.0	0.078	7.2	65.1	72.3	0.110	1.1	10.2	11.3	0.107

TABLE 5.—*Halogen Balance After Cessation of Bromide Therapy (Patient, A. B.)*

	Blood				Spinal Fluid				Urine			
Date	Br.	Cl.	Total	Br./Cl.	Br.	Cl.	Total	Br./Cl.	Br.	Cl.	Total	Br./Cl.
2/18	23.2	59.8	83.0	0.38	12.8	107.6	120.4	0.11	34.7	151.2	185.8	0.22
2/22	19.3	57.3	76.6	0.33	12.8	105.5	118.3	0.12	16.1	58.5	74.6	0.27
2/27	12.0	63.1	75.1	0.19	14.5	101.6	116.1	0.14	21.2	493.7	514.9	0.04
3/ 4	11.2	68.7	79.9	0.16	13.6	104.3	117.9	0.13	14.2	108.2	122.4	0.13
3/ 8	9.2	68.7	77.9	0.13	5.8	113.4	119.2	0.05	8.1	93.7	101.8	0.08
3/18	5.7	74.2	79.9	0.07	6.2	112.7	118.9	0.05	7.3	100.2	107.5	0.07
3/25	3.9	68.6	72.5	0.05	2.5	118.3	120.8	0.02	1.1	23.2	24.3	0.04
4/ 1	4.5	63.6	68.1	0.07	3.8	108.1	111.9	0.03	3.4	78.1	81.5	0.04
6/ 7	0	75.2	75.2	0	+	111.2	111.2	0	—	—	—	

constancy of the finding of a lower ratio for urine than for blood in all the analyses reported indicates that the relative concentrations of chlorine and bromine excreted in the urine do not reflect the concentrations of these elements in blood. On the contrary, there is a small but steady increased rate of excretion of chlorine as compared with bromine.

In order to ascertain the length of time bromine remains in body fluids and the manner of its removal following cessation of bromide therapy, specimens of blood, spinal fluid and urine were obtained for analysis at frequent intervals until bromine had disappeared from the blood of three subjects (A. B., M. McC. and M. D., tables 5, 6 and 7). Consecutive specimens of blood in the three cases show a steadily falling

ratio of bromine-chlorine, which is a resultant of two factors, a decreasing concentration of bromine and a rising concentration of chlorine. It is significant to note that although the initial levels of bromide in the bloods vary from 7.1 to 23.2 milli-equivalents per liter, bromine persists in the bloods of all of the three subjects for forty-four days. The rate of decrease in the ratios expressing relative concentrations of the two halogens is definitely greater for the two subjects A. B. and

TABLE 6.—*Halogen Balance After Cessation of Bromide Therapy (Patient, M. Mc.)*

	Blood				Spinal Fluid				Urine			
Date	Br.	Cl.	Total	Br./Cl.	Br.	Cl.	Total	Br./Cl.	Br.	Cl.	Total	Br./Cl.
2/18	21.4	59.8	81.2	0.35	25.0	91.7	116.7	0.27	5.1	45.1	50.2	0.11
2/22	15.3	59.8	75.1	0.25	10.9	112.5	123.4	0.09	14.5	65.5	80.0	0.22
2/27	13.5	64.4	77.9	0.20	10.7	114.2	124.9	0.09	15.9	168.1	184.0	0.09
3/ 4	10.6	66.0	76.6	0.16	12.2	110.0	122.2	0.11	8.0	67.0	75.0	0.11
3/ 8	8.6	77.5	86.1	0.11	7.6	113.6	121.2	0.06	4.7	22.7	27.4	0.20
3/18	5.5	70.6	76.1	0.07	3.0	118.5	121.5	0.02	3.7	68.7	72.4	0.05
3/25	3.6	78.5	82.1	0.04	3.9	119.9	123.8	0.02	5.8	78.5	84.3	0.07
4/ 1	—	—	....	....	4.7	118.5	123.2	0.03	1.0	28.5	29.5	0.03
6/ 7	0	80.4	80.4	....	0	118.7	118.7	0				

TABLE 7.—*Halogen Balance After Cessation of Bromide Therapy (Patient, M. D.)*

	Blood				Spinal Fluid				Urine			
Date	Br.	Cl.	Total	Br./Cl.	Br.	Cl.	Total	Br./Cl.	Br.	Cl.	Total	Br./Cl.
2/18	7.1	72.8	79.9	0.09	13.1	117.0	130.1	0.11	2.3	35.7	38.0	0.06
2/22	7.1	72.8	79.9	0.09	7.4	115.0	122.4	0.06	5.5	105.5	111.0	0.05
2/27	5.9	76.4	82.3	0.07	4.8	119.0	123.8	0.04	4.2	96.6	100.8	0.04
3/ 4	5.6	74.5	80.1	0.07	6.1	110.0	116.1	0.05	3.6	99.9	103.5	0.03
3/ 8	4.3	78.2	82.5	0.05	5.0	117.0	122.0	0.04	3.4	88.2	91.6	0.04
3/18	4.6	75.0	79.6	0.06	5.5	116.0	121.5	0.04	0.9	14.0	14.9	0.06
3/25	2.4	75.0	77.4	0.03	4.5	114.0	118.5	0.03	3.4	94.0	97.4	0.03
4/ 1	3.2	79.3	82.5	0.04	5.0	114.0	119.0	0.04	2.0	36.0	38.0	0.05
6/ 7	+	80.5	80.5	....	0	117.0						

M. McC., showing larger initial concentrations of bromine than for subject M. D., whose blood originally had much less bromine. Spinal fluids of A. B. exhibit early rises in the ratios due principally to decreases in chlorine of this fluid, and coincident with a rapid fall in the blood ratios. Although M. McC. shows a fairly steady decrease in spinal fluid ratios, in the urine relative concentrations of bromine and chlorine vary markedly in response to two variables, increases in bromine and decreases in chlorine concentration. Apparently, these observations indicate that after cessation of bromide therapy chlorine is substituted for bromine in the blood at a slow rate and at the expense of chlorine of the body fluids, e. g., spinal fluid, and by retardation of

excretion of chlorine. Further, it is of interest to note that the relative concentrations of the two halogens eliminated in the urine do not reflect their concentrations in blood.

SUMMARY

The relative concentrations of bromine and chlorine were determined in whole blood, blood plasma, blood cells, spinal fluid and urine in a group of female epileptic patients who had been receiving bromide-chloride therapy for one year or more.

For each subject, the distribution of bromine between blood cells and plasma was similar to the distribution of chlorine.

The total halogens of the plasma were not increased above the upper normal level for chlorine, but total halogens of the blood cells exhibited increases above the average normal for chlorine of from 15 to 36 per cent.

Total halogens of spinal fluid were not greater than the average normal concentration of chlorine.

In all subjects the concentration of bromine in spinal fluid was less than that in whole blood, and for six subjects the concentration of bromine in spinal fluid varied from 40 to 67 per cent of that found in blood plasma.

The variations noted for the ratio bromine-chlorine of urine from that for blood were between the extremes of from $+4$ to -67 per cent of the blood ratio. Chlorine formed a larger fraction of the total halogens of the urine than that found in blood for fifteen of the sixteen subjects observed.

These changes in the halogen balance of blood, spinal fluid and urine are observed within twenty-four hours after the beginning of bromide therapy. For plasma and spinal fluid, chlorine is replaced by bromine, but apparently in blood cells, addition as well as substitution may take place.

After the withdrawal of bromides, bromine was found in the blood, spinal fluid and urine for forty-four days. At the end of eighty days, the quantities of bromine present in these fluids were too small for quantitative determination with the method used.

Following the withdrawal of bromides, the ratio for bromine-chlorine falls slowly but steadily in blood due both to decreases in bromine and to increases in chlorine concentrations. Fluctuations in the ratios for spinal fluid and urine were observed and have been attributed to the withdrawal of chlorine from these fluids to the blood.

There was observed no evidence that any particular value for the ratio for bromine-chlorine in the blood was optimal for the therapeusis of bromides for all the epileptic patients studied.

ORGANIC FUNCTIONS IN SCHIZOPHRENIA

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As has been emphasized elsewhere,[1] there is need at present for a systematic determination of the organic characteristics of a representative group of schizophrenic patients. The data should be collected in such a way as to assure sufficient homogeneity to permit productive correlation studies among them. A method designed to meet this need has been described in another contribution;[2] to date sixty-four patients have been subjected to the seven months' study schedule therein discussed.

The trends of the study will be summarized by means of a table showing the average value and the variation of each of about fifty functions and by an illustrative case history. The case presented does not purport to conform to the average in all respects—no single case in the series does—but it is representative in showing the degree of variability with which we were confronted, as well as, in general, the deviations from normality that were found to be characteristic.

REPORT OF CASE

History.—H. E. C., an unmarried white man, aged 31, an American, a Protestant, a machinist and farm laborer, born on July 27, 1901, in a small manufacturing town in Massachusetts, the second of eleven siblings, was admitted to the Worcester State Hospital on July 11, 1931. Both grandmothers died of cancer. The paternal grandfather died of "shock." It was said that there were no nervous or mental diseases in the family, though both the paternal and the maternal ancestors were considered "wilful." The father was described as "mentally dull" and "stupid," and as having a poor memory; the mother as fairly intelligent. Two

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With the Collaboration of the Staff of the Research Service.

From the Memorial Foundation for Neuro-Endocrine Research, Boston, and the Worcester State Hospital.

1. (*a*) Hoskins, R. G.: An Analysis of the Schizophrenia Problem from the Standpoint of the Investigator, J. A. M. A. **97**:682 (Sept. 5) 1931. (*b*) Hoskins, R. G., and Walsh, Anna: Oxygen Consumption ("Basal Metabolic Rate") in Schizophrenia: II. Distributions in Two Hundred and Fourteen Cases, Arch. Neurol. & Psychiat. **28**:1346 (Dec.) 1932.

2. Hoskins, R. G.; Sleeper, F. H.; Shakow, D.; Jellinek, E. M.; Looney, J. M., and Erickson, M. H.: A Cooperative Research in Schizophrenia, Arch. Neurol. & Psychiat., to be published.

siblings died in infancy, and one from an injury to the head at 2 years. Eight siblings were living. The father stated that all his children were "silly"; they had never played with other children, having lived on a farm away from other homes. One sister had not worked outside the home because she had not been able to find an occupation that suited her. One brother, who worked on the farm, had a "silly grin" and was said to look "peculiar." Only one sibling was married, and all but he (and perhaps a sister) lived at home.

The birth and early development of the patient had apparently been normal. He had had the usual diseases of childhood, and had had no illness of any consequence in adult life. He started to school at 6 and completed the first year in high school at 15. He attended a boys' trade school for one year, learning carpentry, but was taken out of school because he was needed at home. Progress was satisfactory, and he was said to have enjoyed attending school. He began work at 15 on his father's farm. For the next five years he worked as a farm laborer; then for about eight years he worked as a machinist at $20 per week. His foreman reported him as always quiet and reserved, and as shunning his fellow workmen. Just before he left this job his peculiarities seemed more pronounced than before. From March to October, 1930, he worked on a beet farm. From October, 1930, to admission he was not employed.

In childhood he did not seem to care to play much, but was always working around the farm; he took care of his younger brothers and sisters, and always appeared much older than the rest of the children. He was gentle, but never affectionate. He always had a tendency to be solitary and never knew how to make friends. He talked very little. He was considered self-willed and occasionally became sulky if thwarted, but was generous and good hearted. He rarely made social contacts outside the home circle or at work, and took no part in group activities. He had little recreation other than listening to the radio and reading the newspapers.

He was described as being honest and clean; he did not smoke, drink or swear previous to the onset of the present illness, and was a regular church-goer. He worried considerably about possible future misfortunes for the family, and about a small lesion on his lip, thinking it might be cancer. He said that "everything he wanted to do turned out just the opposite." He always was much discouraged when he met with failure. He was said to have been in love with a girl at the factory where he worked in 1926. She married another man, but even after this the patient bought engagement and wedding rings and continued speaking about marriage to her. Otherwise his heterosexual interests seem to have been greatly restricted. He had been away from home for only one week in his entire life. There was no history of a previous attack of mental disorder.

On April 7, 1929, the patient came home exhausted, hot and worried because he was not perspiring. Following this he was "not quite himself"; he became "jumpy" in his movements and somewhat irritable. About two years before admission, he had imagined that the family had plenty of money; he now said that he did not have to work and was going to buy a number of automobiles.

In September, 1929, he became very irritable; he began to go to the movies every night, and would see the same picture five or six times. He wanted to be doing something all the time and would not rest; he began to express certain dislikes, particularly in regard to the behavior of the family. He also spoke of seeing more people in the room than were actually there.

At Christmas, 1929, he seemed to be afraid of the red lights on the Christmas tree; he kept staring at them and mentioned that the lights stood for rubies. In January he began to speak about going into the movies; he bought some fancy

underwear and a suitcase, and spoke of making arrangements for getting to New York. Whenever the telephone rang he said that he was getting a call from the movies. He kept at work until the end of December, 1929. From January to March, 1930, he sat in a chair silent for long periods of time. He continued to visit the movies frequently. In March, he went to work on a beet farm. For five weeks he worked twelve hours daily, including Sundays, but thereafter for the usual number of hours. In October, he attended a church convention. On returning home he could not be persuaded to enter the house; he said that something terrible was going to happen at 9 o'clock, that his brother was going to be put into a pit and have his eyes taken out; after 9 o'clock he cried and prayed and repeated, "God save us," this lasting throughout the night. For the next two or three days he watched the mirrors, was very frightened and excited, and thought that he was being grabbed. He refused to eat for three days, claiming that the food was poisoned. He was sent to stay with nearby relatives and seemed to recover from this acute episode. From this time on, he sat about the house indifferently, helping in churning the butter and peeling potatoes and taking part in games reluctantly. For three months previous to admission he talked with his hands and did not want to answer questions. About twice a week he became disturbed; he became angry and cursed his brothers. He thought that he ruled the universe, that he was capable of doing almost anything, that everybody knew what he was doing, that he was watched constantly. At times he appeared to be very depressed. At other times he grinned in a silly way. After the family refused to allow him to frequent the movies, he began to read the Bible. For three weeks previous to admission, he imagined that his father was wealthy, and demanded $1,500 of him; he attempted to strike his father when the money was refused. Shortly before admission he imagined that he was an actor in the movies, and after seeing Harry Green on the screen he identified himself with that character. Colors seemed to bother him considerably. After July 4, 1931, he was disturbed; he threw furniture about the house and attempted to strike his parents. He said that he was afraid to talk because he feared his remarks would be broadcast. He spoke of a camera which could take pictures ten miles away and which was photographing him. He believed that the Board of Commerce was behind some of this activity. He said that his brother-in-law (he has none) came into the house by means of electric wiring. He admitted to his mother that some of these ideas were foolish, but he could not get them out of his head. On July 11, 1931, when driving the family car, he became excited, swore, repeated things over and over again and broke the glass in the door. He was then taken to the hospital without resistance.

Examination.—On admission, the patient was neat, clean and tidy, and answered questions readily and coherently. He was oriented for place, but gave the date as March 23, 1930 (it was July 11), and said that he could see the sun shining at 10:30 p. m. No other hallucinations were disclosed. He showed some impairment of memory. He had no apparent insight.

Physically, he was essentially normal, except that the entire upper set of teeth were missing and only six lower teeth were present. Laboratory tests gave essentially normal results.

Mental Status.—On July 15, 1931, the patient was cooperative and seclusive. He did a little work in the ward occasionally, was quiet, grinned in a silly fashion at times, answered questions readily and coherently, talking spontaneously, and seemed abstracted. At times his replies were irrelevant, and he was thought to show a flight of ideas. He seemed somewhat indifferent. He expressed a belief that he was a bad man and could not be trusted, that nobody could go bad unless he went bad, that he would live as long as the world was good, that he could travel

80,000,000 miles an hour through space and electricity, that he could pass through a crack in the floor, that he could hear everything that went on, and that he had told "them" what "they" did not know. He was well oriented in all spheres. He was not cooperative about questions involving memory and general information. He gave the date of his birth as July, 1900 (correctly, July 27, 1901), and said that he began work before he was born. When asked if he was married he replied that "marriage is not allowed in this state." He said that he completed his senior year in high school (correctly, first year high school); that the Declaration of Independence was never made, that the war began in the year 1 over religion, and that the Gulf Stream is where they started playing golf. Judgment was considered poor, and he was thought to have no insight into his condition.

Course.—On July 17, at a staff meeting, the patient seemed to be at a loss to express himself. He blamed his father for many of his difficulties. He said that he had felt for a long time that he was different, that if he had been told in more detail about the differences in the sexes of things he would never have been taken sick and would never have come to the hospital, and that he could not get on with women. He was under considerable emotional tension as he related this and as he talked of his family. He stated that unknown people were annoying him by manipulating his genitals and accusing him of sexual perversions. He seemed to realize that he was ill, but felt that his ideas of persecution were not imagination.

In the wards he was seclusive and reluctant to work. He stood about in corners, looking depressed and anxious. He rarely spoke unless addressed, and was reluctant even to talk to relatives when they visited him; he thought that the hospital was trying "to get something on him." He spoke cryptically of first and second gods. He said: "I'm under space. I'm beyond existence." He said that he had existed since the beginning of time, which was one billion years ago, and that now was the first day the world had existed, and that was why he was there. There seemed to be some change in his delusional ideas from day to day, except that he kept insisting that he was Satan.

On July 20, he was transferred to the research service.

On July 29, the patient was evasive or actually blocked on certain subjects, particularly sex. He gave relevant replies to questions; he had much difficulty in expressing himself accurately, but the stream of talk was coherent. He was slow and deliberate in movements and speech. His facial expression was almost unchangingly dull and stupid. Such emotional reactions as were shown were not incongruous. From the rather elaborate material recorded, a few further items may be excerpted. They afford many suggestions for a "dynamic" analysis, but bear less directly on the theme of this article. The patient discussed various aspects of the case history with considerable freedom, mostly rationalizing them fairly plausibly. He doubted the actuality of his family relationships. He complained about being "mobbed" by girls—referring to hallucinatory scurrilous voices. He expressed further convictions that his family were to be tortured and that he himself frequently was being tortured. He complained that detectives followed him because he had committed many crimes, and that people on the street made remarks about him. His delusions of persecution included also poisoning. The delusions were not systematized. His ideas of influence were of the classic type—mind-reading and outside control. His hallucinations were both auditory and visual; the latter included a vision of God. Possibly a belief he held that he was smothered at night by crude oil and naptha was hallucinatory, possibly delusional. Orientation for time was somewhat defective, but that for person and place was accurate. Remote memory was intact; memories of recent events were not well preserved; retention was fair. School and general information was limited, and he showed

but little contact with current events. Counting and calculation were adequate for simple problems. His capacity for thinking was thought to be rather subnormal. Judgment was markedly defective. He showed a little insight—"Maybe in a way I'm crazy . . . I can't control myself."

Diagnosis and Prognosis.—At a staff conference on July 31, a formal diagnosis was made of schizophrenia, with the majority of the staff favoring the catatonic type. One member preferred the paranoid type. A formal prognosis was given of institutional social adjustment under ordinary care, with considerable possibility of social recovery with intensive therapy.

First Period of Study (August 2 to 27).—No essential change was noted during this period. The mental state at the beginning was considered essentially the same as on July 29, 1931. The patient was fairly friendly and cooperative; he expressed a dislike for the tests; complained about the tests to his relatives, but submitted placidly; refused to swab, but worked well otherwise; spent a great deal of time in a rather manneristic pose about the ward, and always seemed to be self-absorbed and somewhat withdrawn from the environment. The predominant mood throughout was one of indifference. No new ideational content was uncovered. His condition remained fairly constant at the level of institutional adjustment.

First Period of Rest (August 30 to October 24).—During this period the patient became somewhat more silent and inaccessible, though also more observant, and he maintained better contact with his surroundings. The total change, however, was slight and was regarded as inconsequential.

Second Period of Study (October 25 to November 21).—On the whole the patient was submissive to tests, but he did not cooperate actively and tended to be suspicious and to protest about them. His behavior in the ward remained rather stereotyped throughout. He was seclusive, took little part in the activities around him, and was usually to be seen leaning against the wall in a characteristic pose with his legs widespread, apparently observing what was going on. He was orderly and well behaved except for periods of irritability when he obviously wanted to be left alone. He usually did no work in the ward, and swabbed only occasionally, had the attitude that ward work was beneath him and could not be interested in occupational therapy. Throughout the entire period he was obviously antagonistic, suspicious and uncooperative. He frequently railed against the hospital and the tests, but now and then was seen to smile. He seemed to appreciate special attention and to respond to it somewhat. He did not show any great interest in his relatives and always seemed to harangue them at considerable length on the necessity of taking him home. On the whole, his condition at the end of this period of study seemed worse than it was at the beginning. His paranoid reactions had become more acute and the catatonic features less prominent. He was less cooperative, less accessible and less responsive.

Second Period of Rest (Nov. 22, 1931, to Jan. 16, 1932).—Throughout this period the patient's behavior was much the same as during the second period of study, except that he did not show the irritability and antagonism that were marked then, nor did he rail so loudly and bitterly about his confinement in the hospital. He seemed to be accepting hospitalization as something which, though undesirable, was inescapable.

Third Period of Study (January 17 to February 13).—Activity remained at a low level. The patient gave the impression of being dull and uninterested, though fairly observant. He was evasive and found difficulty in expressing himself. His stream of talk showed irrelevance and disconnection. His mood was apathetic, with

traces of suspicion and resentment. He became rather more manneristic in conduct. His mental content was characterized by a wealth of delusions and hallucinations. He had paranoid ideas about the hospital; believed himself followed by a clairvoyant; said that he was surrounded by machinery; reiterated his idea of being a bug, and pointed out his wings to the examining physician; spoke of olfactory hallucinations, of hearing the voices of people who said, "Get out of here" and accused him of stealing; and said that he could see at a distance of 5 miles, that he had seen God in burning bushes and that he could see spirits moving about. It was difficult to determine impulsions, compulsions or obsessions. Orientation seemed defective, but could not be satisfactorily determined. Remote memory seemed defective, and the patient did not appear to have much insight into his condition. Altogether, at this time the paranoid and catatonic features seemed to be about equally prominent.

Summary.—A farm boy, a member of a rather isolated, "queer" family, had succeeded in making a fair vocational adjustment and one abortive attempt at heterosexual adjustment. After a period of growing tension, in which suspiciousness and a certain amount of grandiosity were apparent, at the age of 31 he experienced a panic reaction which brought him to the hospital. At this time he showed such schizophrenic features as irrelevance and delusions of importance and power, of influence, of persecution and of reference. He was rather retarded and apathetic. He had hallucinations in the auditory and visual and perhaps olfactory fields. The case was classified as schizophrenia, with both paranoid and catatonic coloring, the latter predominating. During the three periods of study and the two intervening periods of rest there was relatively little change in the clinical picture, except that the paranoid coloring and emotional tension seemed rather more pronounced in the middle than in the first and last periods.

ORGANIC FINDINGS

In table 1 is set forth a summary in statistical form of the findings in the first fifty-seven cases studied as regards about fifty of the organic variables. Several additional functions were investigated, but the results do not lend themselves to tabular presentation. They included tests of bromide permeability, autonomic irritability, sedimentation rate of the blood and hepatic functions. The vasomotor efficiency was repeatedly studied by the Schneider method, and numerous tests were made of the effect of the blood serum on Lupinus albus. Some of these special studies will be separately and individually reported.

The findings will be taken up seriatim as regards the illustrative case history and they will be compared with the averages for the entire series. The group averaged 31.7 years in age. As indicated by the standard deviation of 7.1, two thirds of the cases fell into the age period from 24.6 to 38.8 years. The youngest patient was 19 and the oldest 45 years of age. The patients had been in the hospital, on

an average, five and nine-tenths years. The figure was thus not entirely representative; the average stay of schizophrenic patients in the state hospitals of Massachusetts is about eleven years. Chronic cases of longer duration were relatively scantily represented. Likewise, we had relatively few cases of the disorder in the early acute stage. The group as a whole represented predominantly the stage at which the psychosis has become well defined, but before deterioration has progressed far —in short, the period at which the manifestations are perhaps most characteristic.

A physical examination was made according to a formal schedule (regional), in which data on one hundred and sixty-four specific features were recorded. In addition, any rare abnormalities not provided for in the schedule were noted. The examination was repeated at the beginning of each of the three subperiods of the study. By and large, the physical findings in the total group were not greatly abnormal. The weight was commonly below prediction, the average "nutritional index" being 84 per cent of normal for the age and height. Few patients in the series were significantly overweight. Occasionally the pubic hair was scanty or of the feminine type of distribution, but for the most part evidences of dysplastic constitution were lacking. The pupils occasionally showed irregularities such as other observers have frequently reported, and cyanosis or coldness of the extremities was often observed; the ordinary reflexes, such as the knee jerk, were also often exaggerated or depressed. The only other gross abnormality that occurred with noteworthy frequency was poor teeth.

Physical Examinations.—H. E. C. was normal physically, except that there were at times oval pupils, a palpable thyroid isthmus, slight cyanosis of the hands and feet, diminished tendon reflexes, an absence of pharyngeal reflexes and slight limitation of motion of the ankles, with transient edema. Twenty teeth were missing, and two of the remainder were carious. Roentgen studies brought out no abnormalities except colonic stasis and a little thickening of both hili of the lungs, suggestive of old healed tuberculosis.

Basal Metabolic Rate.—Table 2 sets forth the data in the case of H. C. L. that are particularly related to the rate of oxygen consumption. These constitute what might be called the "respiratory complex." The "basal rate" recorded is the average of the calculations based on the Harris-Benedict and the Aub-Dubois methods. The rate is expressed directly in percentage of normal rather than by the awkward use of "plus" and "minus" signs. The calculations were independently checked throughout. In each case the attendant recorded a note as to the conduct of the patient during the preliminary period of rest and the metabolimetrist during the tests. The items specifically noted were the degrees of muscular quiescence, of vigilance, of apparent nervous tension and of regularity of pulse and of respiration. The pulse rate was recorded during the first and last portions of the test and the respiratory rate three or four times during its progress.

Rectal Temperature, Pulse Rate and Respiratory Rate.—These were recorded in a routine manner by nurses or attendants twice daily, in the early morning

TABLE 1.—*Means and Variation of Organic Functions Determined in Fifty-Seven Patients in "Seven Months Plan"*

Variable	First Period		Second Period		Third Period		Mean All Three Periods
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	
Age, years	31.7 ± 0.59	7.1 ± 0.42					
Stay in hospital, years	5.9 ±						
Weight, Kg.	62.7 ± 1.0	6.6 ± 0.71	62.5 ± 0.81	9.0 ± 0.58	62.7 ± 1.03	9.8 ± 0.73	62.6
Height, cm.	172.9 ± 0.75	7.2 ± 0.53	172.9 ± 0.75	7.2 ± 0.53	172.9 ± 0.75	7.2 ± 0.53	172.9
Morning temperature (rectal, F.)	97.5 ± 0.02	0.19 ± 0.012	97.6 ± 0.02	0.26 ± 0.022	97.7 ± 0.03	0.31 ± 0.02	97.6
Evening temperature (rectal, F.)	98.9 ± 0.02	0.26 ± 0.016	99.0 ± 0.02	0.19 ± 0.012	99.1 ± 0.02	0.23 ± 0.014	99.0
Basal pulse rate	59.2 ± 0.52	6.14 ± 0.36	59.0 ± 0.63	7.6 ± 0.45	59.4 ± 0.72	7.4 ± 0.51	59.2
Basal systolic pressure, mm. Hg	105.2 ± 0.77	15.78 ± 0.54	99.6 ± 0.70	14.33 ± 0.50	100.5 ± 0.77	15.6 ± 0.54	101.8
Basal diastolic pressure, mm. Hg	65.5 ± 1.33	13.9 ± 0.94	55.5 ± 1.31	13.7 ± 0.93	60.8 ± 0.87	9.15 ± 0.62	60.6
Rate of oxygen consumption, percentage of standard	88.5 ± 0.61	6.9 ± 0.43	88.1 ± 0.92	10.7 ± 0.65	91.4 ± 0.91	9.7 ± 0.64	89.3
Schneider index, score	11.9 ± 0.32	3.28 ± 0.22	12.6 ± 0.23	2.56 ± 0.16	12.0 ± 0.30	2.96 ± 0.21	12.2
Galactose tolerance, Gm.	20.3 ± 0.6	6.7 ± 0.42	22.5 ± 0.9	9.5 ± 0.63	24.3 ± 0.6	6.1 ± 0.42	22.4
Gastro-intestinal emptying time, hours:							
Stomach	4	.....	4	.....	4	.....	4
Ileum	14 ± 1.4	.....	11 ± 0.5	5 ± 0.3	10 ± 0.5	5 ± 0.4	12
Cecum	49 ± 1.3	16 ± 0.9	46 ± 1.0	12 ± 0.7	43 ± 1.1	12 ± 0.8	46
Colon	76 ± 2.2	26 ± 1.5	70 ± 2.0	25 ± 1.4	76 ± 2.3	25 ± 1.6	74
Rectum	96 ± 2.6	31 ± 1.8	84 ± 2.2	25 ± 1.5	82 ± 2.5	27 ± 1.8	87
Urine:*							
Volume, cc.	2,496 ± 101	1,707 ± 71	2,387 ± 87	1,449 ± 62	2,602 ± 120	1,851 ± 85	2,495
Total solids, Gm.	59.8 ± 1.23	20.6 ± 0.87	62.0 ± 1.53	25.3 ± 1.08	69.5 ± 1.50	23.2 ± 1.06	63.8
Total nitrogen, Gm.	10.8 ± 0.2	3.4 ± 0.14	11 ± 0.23	3.7 ± 0.16	12.2 ± 0.19	3.0 ± 0.14	11.3
Urea nitrogen, Gm.	9.3 ± 0.17	2.8 ± 0.12	9.2 ± 0.20	3.3 ± 0.14	10.2 ± 0.18	2.7 ± 0.13	9.6
Creatinine nitrogen, Gm.	0.46 ± 0.008	0.129 ± 0.005	0.49 ± 0.009	0.146 ± 0.006	0.55 ± 0.007	0.116 ± 0.005	0.50
Residual nitrogen, Gm.	0.73 ± 0.02	0.35 ± 0.01	0.67 ± 0.02	0.31 ± 0.01	0.66 ± 0.02	0.31 ± 0.01	0.69

Blood morphology:							
Erythrocytes, thousands	4,900 ± 30	377 ± 22	4,800 ± 38	425 ± 26	5,170 ± 45	458 ± 32	4,957
Leukocytes, per cent	9,650 ± 241	2,833 ± 170	10,420 ± 226	2,570 ± 159	11,360 ± 382	3,894 ± 272	10,477
Polymorphonuclears, per cent	59.5 ± 0.54	6.6 ± 0.4	59.4 ± 0.6	6.8 ± 0.4	60.0 ± 0.7	7.9 ± 0.6	59.6
Lymphocytes, per cent	33.9 ± 0.5	6.4 ± 0.4	32.1 ± 0.5	6.5 ± 0.4	31.6 ± 0.7	7.5 ± 0.5	32.5
Eosinophils, per cent	2.8 ± 0.12	1.5 ± 0.1	2.6 ± 0.13	1.7 ± 0.1	2.5 ± 0.13	1.5 ± 0.1	2.6
Transitionals, per cent	4.2 ± 0.14	1.6 ± 0.1	5.4 ± 0.16	1.9 ± 0.1	6.4 ± 0.18	1.8 ± 0.10	5.3
Basophils, per cent	0.76 ± 0.04	0.62 ± 0.02	0.84 ± 0.04	0.57 ± 0.02	0.56 ± 0.01	0.16 ± 0.01	0.72
Hematocrit reading	45.4 ± 0.31	3.12 ± 0.22	44.0 ± 0.32	3.22 ± 0.22	45.4 ± 0.31	3.11 ± 0.22	44.9
Hemoglobin, Gm. per 100 cc.	15.2 ± 0.07	0.7 ± 0.05	15.2 ± 0.08	0.9 ± 0.05	15.5 ± 0.07	0.9 ± 0.05	15.3
Blood:							
Nonprotein nitrogen, mg.	32.2 ± 0.28	3.3 ± 0.20	33.9 ± 0.28	3.3 ± 0.2	33.1 ± 0.27	2.9 ± 0.19	33.1
Urea nitrogen, mg.	14.3 ± 0.22	2.6 ± 0.15	15.7 ± 0.19	2.2 ± 0.14	14.8 ± 0.17	1.8 ± 0.12	14.9
Amino-acid nitrogen, mg.	6.0 ± 0.03	0.44 ± 0.03	6.0 ± 0.03	0.49 ± 0.02	5.9 ± 0.03	0.41 ± 0.02	6.0
Uric acid, mg.	3.7 ± 0.03	0.52 ± 0.02	4.1 ± 0.03	0.46 ± 0.02	4.1 ± 0.04	0.55 ± 0.03	4.0
Uric acid nitrogen, mg.	1.25 ± 0.01	0.15 ± 0.01	1.36 ± 0.01	0.13 ± 0.01	1.39 ± 0.01	0.16 ± 0.01	1.33
Creatinine, mg.	1.37 ± 0.01	0.09 ± 0.004	1.36 ± 0.01	0.08 ± 0.003	1.32 ± 0.01	0.08 ± 0.004	1.35
Creatinine nitrogen, mg.	0.50 ± 0.00	0.012 ± 0.00	0.49 ± 0.00	0.012 ± 0.00	0.48 ± 0.00	0.012 ± 0.00	0.49
Creatine, mg.	3.89 ± 0.03	0.54 ± 0.02	3.97 ± 0.03	0.55 ± 0.02	3.94 ± 0.04	0.57 ± 0.03	3.93
Creatine nitrogen, mg.	1.18 ± 0.01	0.18 ± 0.01	1.21 ± 0.01	0.20 ± 0.01	1.19 ± 0.01	0.19 ± 0.01	1.19
Residual nitrogen, mg.	9.0 ± 0.35	3.0 ± 0.25	9.0 ± 0.23	2.2 ± 0.18	9.7 ± 0.22	2.4 ± 0.16	9.2
Blood sugar, mg.	99.3 ± 0.8	8.7 ± 0.5	96.5 ± 0.8	8.6 ± 0.5	93.1 ± 0.6	6.8 ± 0.4	95.0
Cholesterol, mg.	146 ± 2.1	24 ± 1.5	161 ± 1.9	23 ± 1.4	166 ± 1.7	17 ± 1.2	158.0
Plasma volume, cc.	2,587 ± 68	451 ± 48	2,546 ± 34	379 ± 24	3,024 ± 44	415 ± 31	2,719
Blood volume, cc.	4,787 ± 111	737 ± 79	4,845 ± 104	694 ± 74	5,097 ± 72	684 ± 51	4,910
Sedimentation rate, mm. per minute	0.22 ± 0.01	0.14 ± 0.01	0.24 ± 0.02	0.19 ± 0.01	0.29 ± 0.02	0.16 ± 0.01	0.25
Arterial oxygen, per cent by volume	17.4 ± 0.26	3.00 ± 0.18	18.0 ± 0.25	2.64 ± 0.17	18.7 ± 0.19	2.00 ± 0.4	18.0
Venous oxygen, per cent by volume	8.7 ± 0.27	3.22 ± 0.47	9.3 ± 0.27	3.06 ± 0.19	9.4 ± 0.29	3.05 ± 0.21	9.1
Arterial carbon dioxide, per cent by volume	50.2 ± 0.34	3.92 ± 0.24	49.2 ± 0.40	4.3 ± 0.28	49.5 ± 0.35	3.63 ± 0.25	49.6
Venous carbon dioxide, per cent by volume	58.5 ± 0.35	4.21 ± 0.25	58.6 ± 0.46	5.3 ± 0.33	58.0 ± 0.40	4.17 ± 0.28	58.4
Arterial p_H	.....	.....	.....	.....	7.42 ± 0.005	0.061 ± 0.004	
Venous p_H	.....	.....	.....	.....	7.35 ± 0.005	0.061 ± 0.004	

* Proportion of catheterized specimens progressively increased from period to period.

before arising and at about 4 p. m. H. E. C.'s morning temperature repeatedly was as low as 97 F. or less. It conformed rather closely to the group average of 97.6 F. The rates that prevailed by the time the metabolism laboratory had been reached (about 9 a. m.) varied from 98.2 to 99.4 F. This fact casts doubt on the actual basality of the patient's condition in the laboratory; the true basal rate may have been lower than that recorded.

TABLE 2.—*Respiratory Complex and Associated Data*

Variable	First Period	Second Period		Third Period	
	8/18/31	11/29/31	11/10/31	1/21/32	2/2/32
Weight, Kg.	73.0	73.6	74.0	68.6	67.6
Volume of lung, per cent	94	50	60	70	98
Nutritional index, per cent	100	101	102	94	93
Height, cm.	175.1				
Sitting height, cm.	93.4				
Sitting height index, cm.	53.3				
	8/5/31	10/29/31		1/21/32	
"B. M. R."	97	71		66	
Blood pressure	96/58	104/70		110/56	
Pulse rate	48-50	44-44		36-42	
Temperature, F.	99.2	98.2		98.8	
Respiratory rate	14-15-14	15-15-14		13-14-14-14	
	8/6/31	10/30/31		1/22/32*	
"B. M. R."	89	76		77	
Blood pressure	122/78	96/60		98/52	
Pulse rate	54-52	44-42		34-38	
Temperature, F.	99.4	98.4		99.0	
Respiratory rate	16-17-16	14-14-13		16-15-16	
	8/7/31	10/31/31		1/23/32	
"B. M. R."	100	72		69	
Blood pressure	116/68	94/50		98/56	
Pulse rate	54-54	40-40		33-35	
Temperature, F.	99.2	98.0		98.8	
Respiratory rate	20-20-20	12-13-13		12-13-13	
	8/18/31	11/10/31		2/2/32†	
"B. M. R."	81	76		71	
Blood pressure	108/80	94/48		110/66	
Pulse rate	44-46	50-50		44-48	
Temperature, F.	98.2	99.0		98.8	
Respiratory rate	20-24-24	12-14-16-15		10-10-11-12	

* "B. M. R." ("basal" metabolic rate): During this test workmen overhead were making a great deal of noise. The patient was restless and wandered about the room before he could be persuaded to lie down. He said that he did not want to take the test.

† "B. M. R.": A great deal of hammering overhead was continuous and disturbing. The patient apparently was calm, however.

On the other hand, the pulse rates obtained during the laboratory tests were comparable with the morning rates in the ward. The ranges in the laboratory were from 33 to 54 and in the ward, from 39 to 54. From this comparison it would seem that an excellent degree of mental and physical relaxation was obtained during the tests. The pulse rate of H. E. C. was distinctly lower than the average for the series, which was 59.2.

The so-called basal systolic blood pressure, as is characteristic of schizophrenic subjects, was remarkably variable. It ranged from 94 to 122 mm. of mercury as compared with an average rate for the entire series of 101.8 mm. Another remarkable feature is the lack of correlation between the blood pressure and the rate of oxygen consumption. Thus on Jan. 21, 1932, with a pressure of 110, the rate

was 66 per cent, while on Nov. 10, 1931, the pressure was 16 mm. lower, but the rate of oxygen consumption was 10 points higher. Such findings are not uncommon in individual cases, though in the series as a whole there is a significant degree of correlation between the two data. But the correlation between the steadiness and frequency of respiratory excursions on the one hand and the rate of oxygen consumption on the other was positive. On Feb. 2, 1932, the excursions were from 10 to 12 per minute and the rate of oxygen consumption was 71, whereas on Aug. 18, 1931, excursions, twice as frequent, i. e., from 20 to 24, were associated with a rate of oxygen consumption of 81.

If one attempts to take into consideration the various accessory findings that may serve as an index of the degree of basality prevailing during the various tests and to deduce the probable value of this patient's actual basal rate, one finds oneself in a quandary. First, there seems to be a systematic gradual fall of the rate during the total period of study. As between the two last subperiods, this drop coincides with a decrease in weight and might be thought to correlate with the patient's state of nutrition. As between the first two subperiods, however, no such relationship is evident.

Changes in weight are likely to be due to changes in assimilation of food. Such changes, especially in the assimilation of protein food, in turn might influence the "specific dynamic action" factor. There is a common belief that the basal rate varies with a level of consumption of protein, through the operation of the "specific dynamic effect" of the circulating amino-acids. In an unpublished analysis of a group of nonpsychotic control subjects we have found such a relationship throughout the range of consumption of protein, but in schizophrenic subjects the correlation between the two features is practically nil. We have not investigated the relationship of foodstuffs other than protein to the rate of the oxygen consumption, but if protein is ineffective, other foodstuffs will also probably prove to be so.

The question whether the shift in the rate of oxygen consumption was due to a change in the severity of the psychosis is expressly reserved for a future report. In the current connection, to ascribe it to such a cause would be to beg the question.

With these conditions in mind, what shall be our selection as representing the patient's basal metabolic rate? As is well known, the errors of technic in this particular test are nearly all in the upward direction. The use of spent soda lime and the aspiration of air around the mouthpiece are the two exceptions. The former error was rigidly excluded by actual tests of the reagent, and the technicians were especially on their guard to forestall the latter. It is altogether probable, therefore, that the lower rates recorded represent the nearest approach to the true basal rate of this patient. Perhaps we can safely state that the patient's representative basal metabolic rate was at least as low as 70 per cent and possibly materially below that level. In this respect the patient is not representative of the series, in which the average rate of oxygen consumption was found to be 89.3 per cent. The problem of oxygen consumption in schizophrenia has been further discussed elsewhere.[1b]

Studies of the Urine (table 3).—These demand one item of special comment, As a routine measure, the patients are kept under surveillance during the entire time of the collection. However, there is an important source of error not thus provided for. Even in the case of the most docile and cooperative patient, one cannot be certain that the initial voiding that precedes the collection has completely emptied the bladder or that at the last voiding urine has not been retained. Accordingly, in every case at least two specimens have been obtained by the use of a catheter, instead of depending on the cooperation of the patient for the first and the last voidings of any given twenty-four hour collection. In addition, the

reliability of the collection can be roughly estimated by the creatinine content. Our patients subsist on a fairly uniform diet, so far as exogenous sources of creatinine are concerned, and reliable collections show this datum fluctuating within fairly narrow limits. Checking the creatinine values of the catheterized specimens against the "voluntary" specimens permits detection of the larger degrees of error. As a fact, we have determined the self-correlation of the creatinine in a large series of analyses, on some noncatheterized specimens, some partly catheterized specimens and some made up entirely of catheterized specimens. The rise in self-correlation as the number of catheterized samples increases is so marked as to indicate that errors of collection in psychotic patients are an important consideration in all quantitative studies of this sort. Unless several consecutive days' collections are made and the findings averaged, voluntary voidings are absolutely unreliable.

Looking first at the values for creatinine nitrogen (table 3) in the six samples analyzed in relation to the last two—catheterized—specimens, it is seen that the first three are entirely unreliable and the fourth probably represents more than a twenty-four hour output. The average value for creatinine of the last two

TABLE 3.—*Studies on the Urine, Twenty-Four Hour Collections*

Variable	First Period		Second Period		Third Period Catheterized Specimens	
	8/16/31	8/18/31	11/8/31	11/10/31	1/31/32	2/2/32
Volume, cc.	1,960	1,560	1,660	1,350	510	1,350
Total solids, cc.	78	58	70	38	36	44
Total nitrogen, cc.	16.9	11.7	11.5	9.7	6.5	8.6
Urea nitrogen, Gm. per 100 cc.	14.3-84.3	9.9 -84.9	8.9 -77.8	7.8 -80.5	4.8 -72.8	6.9 -80.5
Creatinine nitrogen, Gm. per 100 cc.	0.82- 4.8	0.64- 5.5	0.66- 5.3	0.53- 5.5	0.37- 5.7	0.46- 5.3
Residual nitrogen, Gm. per 100 cc.	1.2 - 6.9	0.6 - 5.4	1.6 -13.7	1.1 -10.9	0.5 - 8.0	0.8 - 9.8
Specific gravity	1.017	1.016	1.018	1.012	1.030	1.014
Indican	0	0	0	0	0	0
Urobilinogen	0-0	0-0	S.P.T.-0	0	Faint trace-0	0-0
Albumin	Faint trace	..	..	0	..	Trace
Sediment	Normal	Normal	Normal	Normal	Normal	Normal

specimens is 0.41 Gm., or 5.5 per cent of the total nitrogen. The average volume of the last two specimens was 930 cc., or 38 per cent of the average volume for our total series, which was 2,495 cc.

That the latter value is reliable and essentially representative is shown by a study on forty-four patients from whom the collections were all controlled by catheter. In this group the average volume was 2,602 cc., with a standard deviation of 1,851 cc. The study was controlled by samples from twenty-six normal subjects living in the same environment. Of these, the average volume of the twenty-four hour output was 1,328 cc., and the standard deviation, 629 cc. Thus it appears that the average urinary volume of schizophrenic patients is about twice the normal amount, and the individual variability is three times as great. In individual patients we have often obtained volumes of from 3 to 8 liters a day. In forty-eight of sixty-three patients carefully studied, the average volume was above the conventional high normal of 1,500 cc. These findings were entirely unexpected, and their significance is by no means clear. They suggest a high incidence of disturbed function of either the diencephalon or the posterior lobe of the pituitary gland.

The calculated datum for total solids in H. E. C. was significantly low. The average value for the two catheterized specimens was 40 Gm., as compared with the group average of 63.8 Gm.

In the catheterized specimens the total nitrogen averaged 7.5 Gm., which represents a total protein catabolism of approximately 48 Gm., an amount well below proper maintenance level. If each of the data of the four preceding tests are corrected to a creatinine value of 0.41, the total nitrogen averages 7.6 Gm., representing a total protein catabolism of 49 Gm. We thus have evidence that the patient's protein metabolism was at a subnormal level. In a previous paragraph the evidence was cited that this does not account for the depressed oxygen metabolic rate as it would in a measure in nonpsychotic patients. The residual nitrogen, a constituent that may show high values in certain conditions of disordered metabolism, was at a high normal level. The absence of significant metabolic intoxication suggested by this value is further supported by the consistent absence of indican in the urine. Since auto-intoxication has often been postulated as a cause of schizophrenia, these findings are interesting in their negative aspect. It will be noted in a subsequent paragraph that the patient showed considerable cecal stasis, a condition definitely favorable to putrefactive changes—hence indicanuria—had such been a factor in this case. As regards total nitrogen, the patient was not representative of the group, in which the average value was 11.3 Gm.

TABLE 4.—*Blood Morphology*

	First Period		Second Period		Third Period	
Variable	8/6/31	8/20/31	11/6/31	11/12/31	1/29/32	2/4/32
Erythrocytes	4,410,000	4,520,000	4,210,000	4,160,000	4,630,000	4,180,000
Hemoglobin	....	18.5	14.5	15.0	15.5	14.0
Leukocytes	8,800	10,300	12,800	13,450	15,200	12,500
Polymorphonuclears	54	56.5	67	64.5	63	73.5
Lymphocytes	42	36.5	21.5	27.5	31.5	18
Transitionals	3.5	6	6	4	3	6.5
Eosinophils	0	0.5	4	3	2	2
Basophils	0.5	0.5	1.5	1	0.5	0
Schilling index:						
Senior	....	35.5	57	60.5	61.5	73
Stab cells	....	1	5.5	4	1.5	0.5
Junior	....	0	0	0	0	0
Myelocytes	....	0	0	0	0	0

The faint trace of urobilinogen in the fifth specimen is probably of negligible significance, as is the faint trace of albumin in two samples. The sediments were not abnormal, evidence that genito-urinary disease was not a complicating factor.

The galactose tolerance varied from 20 to 40 Gm. According to Rowe,[3] this is precisely the range in normal subjects. We are unable to interpret the findings beyond suggesting that they may indicate an unsteady hepatic function. The average galactose tolerance for the entire series was 22.4 Gm. as compared with Rowe's average of 30 Gm. for normal males.

Morphology of the Blood.—Studies revealed (table 4) consistently a moderate secondary anemia, the erythrocytes averaging 4,351,000. The patient, a well nourished man, aged 31, would be expected to have a count above 5,000,000. The values for hemoglobin in general were in harmony with the erythrocyte counts. In this regard the patient was not entirely representative of the series in which the average red cell count was 4,957,000; the trend of the group as a whole was downward. There was a moderate and variable leukocytosis, which was characteristic of the series as a whole, averaging 10,477 cells per cubic millimeter. The number of white cells varies with posture and emotional tension, neither of which

3. Rowe, A. W.: The Metabolism of Galactose: I. The Threshold of Tolerance in Normal Adults, Arch. Int. Med. **34**:388 (Sept.) 1924.

was adequately controlled in this series. The normal Schilling formula tends to rule out infection as a cause. The sedimentation rate of the blood in many patients with similar degrees of leukocytosis has failed to give any indication of infection.

Variability in the differential leukocyte counts is striking and unexplained. The polymorphonuclear proportion averaged slightly high in comparison with the average of our seven months' series, in which it was 59.6 per cent. The Schilling index shows an absence of the shift of the formula that is said to indicate intoxication or infection. In this respect, too, the patient was typical of the entire series.

TABLE 5.—*Chemical Analysis of Blood* *

	First Period		Second Period		Third Period	
Variable	8/6/31	8/18/31	10/29/31	11/12/31	1/21/32	2/4/32
Total nonprotein nitrogen	49	34	32	37	36	32
Urea nitrogen	21	14 41	14 44	18 49	20 56	16 50
Amino-acid nitrogen	..	..	5.4 17	6.7 18	5.7 16	5.6 18
Uric acid	4.1	4.2	4.1	4.0	4.4	3.9
Uric acid nitrogen		1.4 4	1.4 4	1.3 4	1.5 4.2	1.3 4.1
Creatinine	1.4	1.4 0.52	1.4 0.52	1.4 0.52	1.3 0.48	1.3 0.48
Creatinine nitrogen		2	2	1.4	1.3	1.5
Creatine	..	3.5	3.6	4.3	3.1	3.7
Creatine nitrogen	..	1.12	1.15	1.38	0.99	1.19
Residual nitrogen	..	3 ..	4 9.53 30	4 9.10 25	2.8 7.33 20	3.7 7.43 23
Sugar	116	95	111	101	91	88
Cholesterol	..	..	176	..	148	148

	11/6	1/29
Plasma volume	2,791	3,475
Blood volume	5,260	5,620
p_H		A. 7.33, V. 7.23
Arterial oxygen	17.24	16.96
Venous oxygen	6.39	6.72
Arterial carbon dioxide	51.18	49.28
Venous carbon dioxide	64.55	60.25

* The results are in milligrams per hundred cubic centimeters, and, in the case of nitrogen fractions, in percentage of the total.

Analyses of the Blood.—The findings (table 5) for the most part were not remarkable either in the case cited or in the entire series and call for little comment. They were mostly within normal limits but showed a rather marked shift from test to test. The total nonprotein nitrogen of the patient averaged 37 mg., as compared with the group average of 33 mg. The uric acid, determined by the Francke-Benedict method for this patient, was 4.1 mg.; the average for the group was 4 mg. The average for thirty-one normal control subjects was 3.9 mg. The cholesterol content trended somewhat low, as did the average value for the entire series, namely, 158 mg. per hundred cubic centimeters. A rather striking anomaly was the low value of the venous oxygen. This seems to indicate slowing of the peripheral circulation; this is borne out, in the case under consideration, by the high venous carbon dioxide, but in other cases the data were not so consistent. In view of recent attempts to explain the psychosis in terms of dispersion of the circulating and the brain cell colloids, it is of interest that the p_H of the blood in this patient, as in the whole series, was normal.

Cardiovascular Tests.—The data (table 6) suggest why the characteristic basal hypotension of schizophrenic patients has commonly been overlooked. The tests were made in the afternoon when the patient was actively adjusting to his environment. The systolic blood pressure ranged from 115 to 131 mm. of mercury, whereas the basal blood pressure was below 100 mm. Were the afternoon values the only ones available, the patient would unquestionably be reported as having a normal blood pressure. This would be borne out by the Schneider index, which was within normal limits—indeed well toward the upper normal value that is shown by trained athletes in the pink of physical fitness. We do not regard the favorable showing in these tests as truly mirroring the degree of physical fitness of the patients.

Hepatic Function.—This was tested in several ways. Bromsulphthalein excretion was not affected in the case of H. E. C., the findings being consistently normal as in practically all the cases. In two of the six twenty-four hour samples of urine, the slightest possible trace of urobilinogen was found. McClure's test

TABLE 6.—*Cardiovascular Test*

Variable	First Period 10/5/31	Second Period 11/6/31	Third Period 1/29/32
Systolic pressure, mm.	115	131	125
Diastolic pressure, mm.	75	84	85
Pulse rate	48	45	40.5
Schneider index	15–16	12–15	12

TABLE 7.—*Gastro-Intestinal Motor Functions*

Emptying Time, Hours	First Period 9/25/31	Second Period 11/17/31	Third Period 2/9/32
Stomach	4	4	4
Ileum	12	9	48
Cecum	72	72	72
Colon	168	96	120
Rectum	168	120	120

was carried out on two occasions within a few months after the seven months' study was completed. With both tests the cholesterol was normal in amount. In the first collection the furfural number was low, and the level of the bile pigments was normal. At the second examination, the furfural number was normal and the pigments low. We have found in many cases of schizophrenia that the biliverdin content is low, with the findings normal in other respects. This suggests a lowering of oxygenation processes. The Graham test findings, van den Bergh reaction and icteric index were all normal at the time of testing.

On the basis of these tests, we are perhaps justified in assuming an inconstant diminished level of hepatic efficiency. Various functions of the liver were apparently affected at different times. The same statements can be made regarding the series as a whole.

Gastro-Intestinal Function.—Roentgen studies of H. E. C. (table 7) indicated normal motor functions in the upper part, but fairly marked stasis in the lower part of the bowel. The prolonged retention of barium sulphate in the ileum in the third period is anomalous and not explained. As compared with the average values for the entire series, the delay is accentuated in both the cecum and the colon, averaging seventy-two and one hundred and twenty-six hours, respectively, in the one case,

and forty-six and seventy-four hours in the other. The retention of the rectal contents averaged one hundred and thirty-six hours in the patient and eighty-seven hours in the total series. The constipation thus indicated is probably of little or no physiologic importance. Altogether, according to these findings, the gastrointestinal motor functions of schizophrenic patients are not significantly abnormal above the cecum, but from this level down a considerable degree of sluggishness commonly occurs. To that extent the old idea of intestinal auto-intoxication as a characteristic of the psychosis is supported. However, the stasis is rarely accompanied by significant putrefactive activity, so far as can be judged by the formation of indican; we have made routine tests for indicanuria, but seldom have obtained positive responses. Furthermore, Macht's test with Lupinus albus has failed to disclose any significant evidence of intoxication. As further negative evidence we may cite the fact that neither saline cathartics nor prolonged treatment with Bacillus acidophilus has shown any noteworthy beneficial effect on the symptomatology in small groups in which they were employed systematically.

COMMENT

The evidence brings out two sorts of abnormality as characteristic of schizophrenia. Most noteworthy, perhaps is the high degree of vari-

TABLE 8.—*Extreme Values in Case Reported*

Variable	Values	
Rate of oxygen consumption, per cent	100	66
Blood pressure, mm.	122	94
Pulse rate	54	34
Temperature (rectal), F.	99.2	96.6
Volume of urine, cc.	1,960	510
Galactose tolerance, Gm.	40	20
Erythrocytes	4,160,000	4,630,000
Leukocytes	15,200	10,300
Lymphocytes, per cent	42	18
Blood nitrogen, mg.	49	32
Blood sugar, mg.	116	88
Emptying time of colon, hours	168	96

ability of many of the bodily functions. In table 8 are noted the extreme values in a few of these, as exemplified in H. E. C. If we had had available only single tests, the patient might have been characterized, as a matter of random chance, by values falling anywhere between the extremes noted. He thus might have seemed to be either essentially normal, physiologically, or grossly abnormal. The findings serve to bring into sharp relief the futility of researches based on single tests, so far as individual patients are concerned. Such tests are valid solely for the purpose of striking group averages in which high and low values compensate.

Not only is the average schizophrenic patient a highly variable person as regards physiologic functions, but certain of these are basically abnormal. Cannon pointed out as a fundamental biologic principle the fact that efficiency—indeed, even survival—is dependent on the operation of a multiplicity of mechanisms for the maintenance of a "steady

state" in the organism. This principle he has called "homeostasis."[4] In 1931, on the basis of data then available, the prediction was ventured that schizophrenia would prove to be characterized by abnormal homeostasis.[1a] It was suggested that this might involve abnormalities in the response to stimuli as well as organization at displaced (pathologic) levels. The data obtained in the current study seem to substantiate both aspects of the suggestion. Further discussion of this generalization will be deferred until the findings regarding the various functions have been reported in further detail.

SUMMARY

An epitomized account is given of the results of a study of the physiologic functions in schizophrenia as brought out by repeated tests on fifty-seven male subjects over a period of seven months. An illustrative case history is included.

The average age of the patients was 31.7 years, and the period of hospitalization, five and nine-tenths years. Recent acute cases as well as old chronic cases were sparsely represented.

Grossly, the patients in most respects were organically normal. They averaged 16 per cent underweight and as a group showed a high incidence of poor circulation of the skin, irregularities of the pupils, abnormal reflexes and poor teeth.

The blood pressure, the rate of oxygen consumption and, to a slight extent, the pulse rate were basically depressed. The level of protein metabolism showed no significant correlation with the rate of oxygen consumption as it did in a control series. This group of findings serves to indicate hypometabolism as a characteristic condition.

The urinary constituents were normal in amount, as was the distribution of the nitrogenous components, but the total volume was twice the normal amount and the variability of output three times as great as in a control series of samples from normal subjects. This finding suggests abnormal functioning of the diencephalon or of the posterior lobe of the pituitary gland.

The galactose tolerance was notably variable, from 20 to 40 Gm. in most cases, with a group average of 22.4 Gm. as compared with a reported normal average of 30 Gm. The blood sugar during fasting, on the other hand, was strictly normal in both average and range.

The blood pictures were characterized by a high incidence of moderate secondary anemia and leukocytosis. The average red and white cell counts were 4,957,000 and 10,477, respectively. The differential counts averaged substantially normal. The sedimentation rate and Schilling

4. Cannon, W. B.: Organization for Physiological Homeostasis, Physiol. Rev. **9**:399 (July) 1929.

indexes were commonly normal. The chemical constituents of the blood were unusually variable in individual cases, but the averages were mostly normal. The cholesterol content ranged slightly low. In individual cases the venous oxygen was strikingly low, but the average was substantially normal.

The Schneider index was normal, giving a factitious appearance of physical fitness.

The functional efficiency of the liver, tested in a variety of ways, indicated a variable and inconsistent inefficiency in a considerable proportion of the cases.

Nearly all of the functions studied showed high individual variability.

CONCLUSION

As regards homeostasis, schizophrenia is characterized by two deviations from normality. The ability to maintain the "steady state" is diminished, and some functions are basically displaced in an upward, others in a downward, direction.

BLOOD-CEREBROSPINAL FLUID BARRIER IN ALCOHOLIC DISORDERS

AND IN SCHIZOPHRENIA COMPLICATED BY ALCOHOLISM; DISTRIBUTION RATIOS OF BROMIDE, CALCIUM, SUGAR AND CHLORIDES

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Within recent years investigations of the blood-cerebrospinal fluid barrier have occupied a prominent place in psychiatric research. Various methods have been developed for studying the functional state of the barrier. One of the procedures used most frequently for this purpose is the test devised by Walter [1] for determining the ratio of distribution of bromide between the blood and the cerebrospinal fluid. Some of the advantages and disadvantages of this method have been discussed in previous communications.[2] Apparently, few workers have attempted to test its accuracy by carrying out parallel experiments with other procedures for estimating the bromide content of the two fluids. Nevertheless, the consistent deviations from the normal that have been discovered in certain psychoses by means of Walter's method cannot be dismissed as purely accidental. Even though their significance may still be obscure, such deviations are of sufficient interest to render further studies in this field desirable. Before the bromide method can be properly evaluated, it will be necessary to accumulate a large number of observations in as many types of mental disease as possible. Some psychoses have already been dealt with in considerable detail,[3] but many of the less common ones have received little attention. In the present

From the Foxborough State Hospital.

1. Walter, F. K.: Studien über die Permeabilität der Meningen, Ztschr. f. d. ges. Neurol. u. Psychiat. **95**:522, 1925.

2. (*a*) Malamud, W.; Fuchs, D. M., and Malamud, N.: Barrier Between the Blood and the Cerebrospinal Fluid: I. Changes in Permeability in Mental Diseases, Arch. Neurol. & Psychiat. **20**:780 (Oct.) 1928. (*b*) Malamud, W., and Rothschild, D.: Barrier Between the Blood and Cerebrospinal Fluid: III. Distribution Ratio of Bromides in Schizophrenias, ibid. **24**:348 (Aug.) 1930. (*c*) Rothschild, D., and Malamud, W.: The Blood-Cerebrospinal Fluid Barrier in Manic-Depressive Psychosis: Ratios of Distribution of Bromide, Calcium, Sugar and Chlorides, ibid. **26**:829 (Oct.) 1931.

3. Malamud and Rothschild.[2b] Rothschild and Malamud.[2c]

communication we are reporting the results obtained with the bromide test in the alcoholic group of mental disorders. In addition, observations made on schizophrenic patients who were intemperate were included for purposes of comparison.

A study of alcoholic conditions seems to be of particular interest for the light that it may throw on the effect of toxic substances on the blood-cerebrospinal fluid barrier. However, the information available on this subject is scanty. Hauptmann [4] determined the ratio of distribution of bromide between the blood and the spinal fluid in twenty cases of alcoholic disorder. Twelve patients were examined by Walter [5] and twenty-eight by von Rohden.[6] The bromide test was used by Gordy and Smith [7] in fourteen cases and by Büchler [8] in nine. To our knowledge, detailed investigations of the exchange of other substances between the blood and the cerebrospinal fluid have not been made in alcoholic psychoses. In this connection it should be remembered that Fleischhacker and Scheiderer [9] have shown that the ratio of distribution of bromide may be increased or decreased independently of the behavior in this respect of some of the normal constituents of the blood. Hence, in studying the functional state of the barrier it would not seem advisable to rely exclusively on the results obtained with Walter's method. We have therefore supplemented the bromide test in the more recent work by determining the ratios of distribution of calcium, sugar and chlorides between the blood and the cerebrospinal fluid.

MATERIAL AND METHODS

Our material was made up of fifty-three cases of alcoholic mental disorder, ten of which have been reported previously,[2a] and fourteen cases of schizophrenia complicated by alcoholism. There were seventeen cases of delirium tremens, eleven of Korsakoff's psychosis, eight of chronic alcoholism and seventeen of alcoholic hallucinosis. It should be noted that the diagnosis of chronic alcoholism was reserved for cases in which definite evidence of a psychosis, apart from a certain

4. Hauptmann, A.: Zur Pathogenese alkoholischer Geistes- und Nervenkrankheiten an der Hand von Untersuchungen über die Blut-Liquorschranke, Deutsche Ztschr. f. Nervenh. **100**:91, 1927.

5. Walter, F. K.: Die Blut-Liquorschranke, Leipzig, Georg Thieme, 1929.

6. von Rohden, F.: Ueber die diagnostische Bedeutung der Walterschen Permeabilitätsreaktion, Arch. f. Psychiat. **87**:797, 1929.

7. Gordy, S. T., and Smith, S. M.: The Permeability of the Hemato-Encephalic Barrier as Determined by the Bromide Method, Arch. Neurol. & Psychiat. **24**:727 (Oct.) 1930.

8. Büchler, P.: Beiträge zur Permeabilitätsschwankung der Geistes- und Nervenkrankheiten, Arch. f. Psychiat. **77**:613, 1926.

9. Fleischhacker, H., and Scheiderer, G.: Ueber die "Permeabilitätsquotienten" für Calcium, Chlor (Gesamthalogene) und Brom und ihre gegenseitigen Beziehungen bei endogenen Geisteskrankheiten, Monatschr. f. Psychiat. u. Neurol. **75**: 346 (May) 1930.

amount of deterioration, had at no time been observed. All but two of the patients belonged to the male sex. Cases in which there were indications of acute infection or disease of the nervous system caused by extraneous factors were excluded from the groups presented here.

The ratio of distribution of bromide between the blood and the cerebrospinal fluid was determined in all cases. Hauptmann's [10] modification of Walter's method was used. As the procedure has been described in detail in an earlier communication,[2a] only a brief outline is given here. Sodium bromide is administered orally in the proportion of 0.01 Gm. per pound of body weight three times daily for five days. After an interval of about eighteen hours, blood and cerebrospinal fluid are removed as nearly simultaneously as possible. This is done with the patient in a fasting condition. The proteins are precipitated in both fluids with trichloracetic acid. Gold chloride is added to the filtrates, thus causing the formation of gold bromide. This is yellowish brown, the intensity of the color varying with the concentration of the bromide. By examining the two solutions in a colorimeter, a ratio is obtained which represents the proportion of bromide in the blood as compared with that in the spinal fluid. In normal persons the concentration of bromide in the blood is about three times greater than that in the spinal fluid. The normal ratio of distribution is therefore about 3, with fluctuations, according to Malamud, Fuchs and Malamud,[2a] from 2.8 to 3.2. According to other investigators, however, the range is from 2.9 to 3.3. In the present communication values under 2.8 are considered low and hence indicative of a relative increase in the bromide in the cerebrospinal fluid. Ratios between 3.2 and 3.3 are regarded as borderline but not definitely abnormal. Values above 3.3 are looked on as high. They denote a relative decrease in the bromide in the spinal fluid.

For the purposes of the present investigation, Walter's method had the disadvantage that the bromide had to be administered for five days before the test could be carried out. Hence it was not possible to perform the examinations during the periods in which alcohol was being taken. In fact, the psychotic symptoms had frequently disappeared by the time the determinations were made. Therefore, in analyzing our observations close attention was paid to the date on which the spinal fluid was withdrawn, particularly as regards its relation to the onset and course of the mental disorder.

The ratios of distribution of calcium, sugar and chlorides were calculated by making parallel determinations of the amounts of these substances present in the blood and spinal fluid. The method employed for calcium was the Clark-Collip modification of the Kramer-Tisdall procedure.[11] In the majority of cases sugar was estimated by Folin's 1930 modification [12] of the Folin-Wu method [13] of 1929. The Van Slyke [14] procedure was used for chlorides. In all cases the cells in the

10. Hauptmann, A.: Untersuchungen über die Blut-Liquorpassage bei Psychosen, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:332, 1926.

11. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Calcium With a Suggested Modification, J. Biol. Chem. **63**:461, 1925.

12. Folin, O.: Unlaked Blood as a Basis for Blood Analysis, J. Biol. Chem. **86**:173, 1930.

13. Folin, O.: Two Revised Copper Methods for Blood Sugar Determination, J. Biol. Chem. **82**:83, 1929.

14. Van Slyke, D. D.: The Determination of Chlorides in Blood and Tissues, J. Biol. Chem. **58**:523, 1923.

spinal fluid were counted, tests for globulin and albumin or total protein were performed, and the colloidal gold and Wassermann reactions were determined. These observations were not recorded in the tables unless abnormal results were obtained.

RATIO OF DISTRIBUTION OF BROMIDE IN ALCOHOLIC DISORDERS

The majority of the patients with delirium tremens showed normal ratios for the distribution of bromide (table 1). In five cases the initial determinations yielded values below 2.8. Figures above 3.3 were obtained in three cases. Eight of the patients with Korsakoff's psychosis exhibited ratios below 2.8 when the first bromide test was performed (table 2). Low ratios were also observed in most of the cases of chronic alcoholism (table 3). Figures above 3.3 were not found in these two groups. The results of the determinations in alcoholic hallucinosis were similar to those in delirium tremens (table 4). The initial ratios were low in six cases and definitely high in two cases.

Almost all the patients with low or normal ratios exhibited typical clinical pictures, whereas most of those with high figures presented atypical mental symptoms. Low ratios were generally obtained in the former group when the determinations were made within a comparatively short time following the excessive use of alcohol. On the other hand, the ratios were usually normal when the tests were performed only after longer periods of abstinence. In the majority of cases in which examinations were made on two or more occasions, the first determinations yielded lower figures than the later ones. These results were observed regardless of the presence or absence of psychotic manifestations at the time of investigation. There were two exceptions (patients 7 and 9, table 1) which showed that values above 2.8 may be found as early as nine or ten days after the cessation of drinking. In both instances, however, the ratios were near the lower limit of normal. Other apparent exceptions can be accounted for by the fact that the patients in question had been abstinent for some time prior to their admission to the hospital. There was no definite relation between the duration of the acute psychosis and the ratio of distribution of bromide.

None of the patients with high ratios showed an appreciable degree of permanent mental impairment. Here personal factors seemed more important, and the toxic element less prominent, than in the cases with low or normal values. The most pronounced deterioration was observed in the patients with Korsakoff's psychosis, for whom the first bromide test yielded figures below 2.8. While physical signs of involvement of the nervous system were frequent in this group, the severest polyneuritis occurred in the three patients with the lowest initial ratios (18, 19 and 20, table 2).

TABLE 1.—*Distribution Ratio of Bromide in Delirium Tremens*

Patient	Age	Date of Admission	Date of Lumbar Puncture	Distribution Ratio of Bromide	Previous Attacks	Other Observations
1	35	11/ 8/29	11/23/29	2.43	Several	Moderate deterioration; achilles reflexes diminished
2	33	8/24/30	9/11/30	2.56	1	Moderate deterioration; pupils react sluggishly to light and in accommodation; marked tremors
3	53	4/ 9/27	4/14/27	2.61	0	Moderate deterioration; pupils react sluggishly to light and in accommodation; tremors
4	48	1/20/31	2/13/31 3/25/31	2.70 3.30	Several	Considerable deterioration; intolerant to alcohol; slight tremors
5	59	7/14/29	8/16/29	2.77	Several	Considerable deterioration; left achilles reflex absent; tremors
6	60	3/ 7/28	3/29/28	2.81	Several	Considerable deterioration; pupils react sluggishly to light; tremors
7	42	4/23/28	5/ 3/28	2.85	0	Slight deterioration
8	47	9/14/27	10/24/27	2.89	Several	Moderate deterioration; intolerant to alcohol; epileptiform seizures
9	36	12/13/27	12/22/27	2.90	0	Moderate deterioration
10	69	3/17/27	4/28/27	3.00	0	Slight deterioration; psychosis followed operation for hernia
11	47	5/11/29	1/ 9/30	3.08	0	Considerable deterioration; pupils react sluggishly to light; slight tremors
12	56	11/24/26	4/18/27	3.12	1	Moderate deterioration
13	42	6/19/30	7/14/30	3.24	0	Slight deterioration; tremors; atypical clinically
14	50	2/ 5/31	2/20/31	3.30	0	No deterioration; slight tremors; atypical clinically
15	42	10/20/28	10/29/28	3.35	1	No deterioration; slight tremors
16	46	7/12/28	8/ 2/28	3.41	0	No deterioration; atypical clinically; colloidal gold curve 0001221000
17	32	1/11/28	2/ 2/28	3.47	0	No deterioration; slight tremors; atypical clinically

TABLE 2.—*Distribution Ratio of Bromide in Korsakoff's Psychosis*

Patient	Age	Date of Admission	Date of Lumbar Puncture	Distribution Ratio of Bromide	Previous Attacks	Other Observations
18	44	2/15/32	3/ 3/32 8/ 4/32	1.93 2.21	0	Marked deterioration; tendon reflex absent; bilateral foot-drop with sensory impairment
19	62	3/25/29	4/ 4/29 1/16/30 2/13/30 5/15/30	2.16 2.62 2.85 2.79	0	Very marked deterioration; pupils react sluggishly to light; tremors; patellar and achilles reflexes absent on right, diminished on left; psychosis precipitated by slight injury to head
20	64	10/11/27	10/24/27	2.25	0	Marked deterioration; tendon reflexes absent; atrophy of calf muscles; cirrhosis of liver
21	66	12/20/28	1/24/29	2.32	0	Moderate deterioration; tremors; psychosis precipitated by exposure to cold and frostbite
22	57	7/25/29	8/16/29	2.32	0	Considerate deterioration; pupils react sluggishly to light and in accommodation; slight tremors
23	57	8/10/26	3/30/27 8/19/31	2.69 2.85	2	Marked deterioration; patellar and achilles reflexes absent
24	51	7/ 7/28	5/15/30	2.70	0	Marked deterioration; tremors; psychosis precipitated by injury to head
25	50	6/27/27	9/21/27	2.78	Unknown	Considerable deterioration; tremors
26	56	7/ 9/26	3/30/27	2.81	0	Considerable deterioration; patellar and achilles reflexes absent; psychosis precipitated by injury to head
27	52	1/ 2/30	1/30/30	2.89	0	Considerable deterioration; pupils react sluggishly to light; achilles reflexes absent
28	51	1/23/11	7/11/27 8/11/27 1/17/29 5/11/29	3.02 3.00 3.00 3.07	0	Considerable deterioration; Wassermann reaction of blood positive; that of spinal fluid negative; colloidal gold curve 0011100000

TABLE 3.—*Distribution Ratio of Bromide in Chronic Alcoholism*

Patient	Age	Date of Admission	Date of Lumbar Puncture	Distribution Ratio of Bromide	Previous Attacks	Other Observations
29	59	8/ 4/29	8/ 9/29	2.55	0	Slight deterioration; pupils react sluggishly to light; admitted in acutely intoxicated state; mild diabetes
30	35	12/29/27	1/ 5/28	2.63	0	Slight deterioration; admitted in acutely intoxicated state
31	68	10/18/30	11/ 6/30	2.70	0	Moderate deterioration; admitted in acutely intoxicated state; pupils react sluggishly to light and in accommodation; achilles reflexes diminished
32	49	6/11/29	6/20/29	2.70	0	Slight deterioration; admitted in acutely intoxicated state; intolerant to alcohol; tremors
33	60	6/ 5/27	6/10/27	2.76	0	Moderate deterioration; tremors
34	51	2/26/25	3/30/27	2.90	0	Considerable deterioration
35	41	11/ 6/30	11/28/30	3.15	0	Slight deterioration
36	69	8/23/28	1/ 3/29	3.22	0	Moderate deterioration; patellar reflexes diminished; left achilles reflex diminished, right absent; abstinent for several years previous to admission

TABLE 4.—*Distribution Ratio of Bromide in Alcoholic Hallucinosis*

Patient	Age	Date of Admission	Date of Lumbar Puncture	Distribution Ratio of Bromide	Previous Attacks	Other Observations
37	67	7/25/29	8/16/29	1.92	3	Slight deterioration; intolerant to alcohol; slight tremors
38	48	4/ 3/28	4/19/28 1/ 2/30	2.11 2.74	Probably several	Marked deterioration; achilles reflexes diminished; pupils react sluggishly to light
39	49	1/13/31	1/29/31	2.55	0	Slight deterioration; slight tremors
40	42	10/14/27	11/26/27 4/ 5/28	2.64 3.07	1	Moderate deterioration; Wassermann reaction of blood positive; that of spinal fluid negative; colloidal gold curve 0001111000
41	46	5/31/28	7/12/28 1/ 2/30	2.70 2.84	Unknown	Marked deterioration; slight tremors
42	46	7/19/28	8/ 2/28	2.77	Unknown	Slight deterioration; colloidal gold curve 0001220000
43	42	6/16/30	11/13/30	2.85	Probably 1	Considerable deterioration; intolerant to alcohol; slight tremors; pupils react sluggishly to light
44	45	7/ 8/27	8/29/27	2.88	Probably several	Considerable deterioration; previous attacks of delirium tremens
45	45	9/ 4/30	9/18/30	2.97	0	Considerable deterioration; pupils react sluggishly to light; patellar reflexes exaggerated; achilles reflexes diminished; some ataxia and impairment of sensation in lower extremities
46	40	2/ 5/31	4/ 8/31	3.00	Probably several	Moderate deterioration; pupils react sluggishly to light
47	48	12/10/26	4/14/27	3.03	Several	Moderate deterioration; intolerant to alcohol; Wassermann reaction of blood positive, of spinal fluid negative; colloidal gold curve 0012210000
48	43	12/ 8/27	12/29/27	3.06	1	Slight deterioration; previous attack of delirium tremens
49	22	4/27/27	5/ 9/27	3.09	0	Slight deterioration
50	47	12/19/29	1/16/30	3.15	Several	Slight deterioration; atypical clinically
51	36	4/25/30	6/ 5/30	3.29	0	Slight deterioration
52	37	12/14/30	1/ 2/31	3.45	1	No deterioration; atypical clinically; previous attack of pathologic intoxication
53	44	6/27/31	7/15/31	3.64	0	No deterioration; atypical clinically

RATIOS OF DISTRIBUTION OF CALCIUM, SUGAR AND CHLORIDES IN ALCOHOLIC DISORDERS

The ratio of calcium in the blood to that in the spinal fluid was estimated in nineteen of the patients for whom the bromide test was performed. In most of these the distribution of sugar and chlorides between the two fluids was also investigated. The data are arranged in table 5. Since the blood usually contains about twice as much calcium as the spinal fluid, the normal ratio of distribution is about 2. According to Fleischhacker and Scheiderer,[9] the normal range is from 1.8

TABLE 5.—*Comparison of Distribution Ratios of Calcium, Sugar, Chlorides and Bromide*

Patient	Distribution Ratio of Bromide	Serum Calcium, Mg. per 100 Cc.	Spinal Fluid Calcium, Mg. per 100 Cc.	Distribution Ratio of Calcium	Blood Sugar, Mg. per 100 Cc.	Spinal Fluid Sugar, Mg. per 100 Cc.	Distribution Ratio of Sugar	Blood Sodium Chloride, Mg. per 100 Cc.	Spinal Fluid Sodium Chloride, Mg. per 100 Cc.	Distribution Ratio of Chloride	Diagnosis
18	1.93	10.0	5.3	1.88	....	....	....	...	...	....	Korsakoff's psychosis
1	2.43	11.0	5.6	1.96	....	....	....	...	...	....	Delirium tremens
39	2.55	10.7	4.8	2.24	75.4	43.0	1.75	559	719	0.78	Alcoholic hallucinosis
2	2.56	11.3	5.5	2.05	76.0	40.0	1.90	600	732	0.82	Delirium tremens
19	2.62	11.4	5.2	2.19	87.0	64.5	1.34	...	...	....	Korsakoff's psychosis
	2.85	11.2	5.2	2.15	85.0	64.4	1.30				
	2.79	10.5	5.6	1.88	81.6	55.5	1.47	580	705	0.82	
4	2.70	9.8	5.8	1.69	69.2	52.3	1.32	589	713	0.83	Delirium tremens
	3.30	9.3	5.3	1.75	95.0	66.0	1.43	580	713	0.81	
24	2.70	10.9	5.4	2.02	84.3	76.1	1.10	594	720	0.82	Korsakoff's psychosis
31	2.70	9.2	4.8	1.92	91.1	55.6	1.63	599	725	0.83	Chronic alcoholism
38	2.74	12.3	5.7	2.16	....	....	....	...	...	....	Alcoholic hallucinosis
41	2.80	10.9	5.1	2.14	....	....	....	...	...	....	Alcoholic hallucinosis
43	2.85	10.5	5.0	2.10	94.0	62.5	1.50	606	719	0.84	Alcoholic hallucinosis
23	2.85	10.1	5.2	1.94	....	....	....	...	...	....	Korsakoff's psychosis
46	3.00	9.3	4.8	1.93	85.0	47.0	1.80	580	710	0.81	Alcoholic hallucinosis
11	3.08	11.0	5.2	2.11	100.0	57.0	1.76	...	...	....	Delirium tremens
35	3.15	....	...	....	76.9	52.9	1.45	568	693	0.82	Chronic alcoholism
13	3.24	10.8	4.7	2.29	....	....	....	...	...	....	Delirium tremens
51	3.29	10.4	5.3	1.95	76.7	54.9	1.37	587	716	0.80	Alcoholic hallucinosis
14	3.30	10.0	4.8	2.07	81.6	70.0	1.16	549	666	0.82	Delirium tremens
52	3.45	9.0	4.5	1.98	84.5	47.0	1.79	605	719	0.84	Alcoholic hallucinosis
53	3.64	11.2	5.0	2.25	80.0	58.0	1.37	602	731	0.82	Alcoholic hallucinosis

to 2.2. Our figures were within these limits in 79 per cent of the group. One patient exhibited a low ratio for the distribution of calcium. Ratios above 2.2 were obtained in three cases, two of which (patients 13 and 53) were atypical clinically. This is of interest in view of the fact that most of the high ratios for bromide occurred in such cases. Apart from this, a study of the results of the determinations of calcium failed to reveal anything that resembled the observations made with Walter's test. The various groups discussed here did not show any significant differences in their average calcium values.

Determinations of sugar were performed in fourteen cases (table 5). It is difficult to evaluate our observations owing to the lack of agreement as to what constitutes the normal ratio of distribution

of the substance in question. This is probably due to the fact that the sugar level of the blood may show rapid fluctuations which are reflected in the spinal fluid only after a latent period. In a recent article, however, Fremont-Smith and his co-workers [15] came to the conclusion that a nine to twelve hour fast preceding lumbar puncture with the patient in bed, gives reasonable assurance of equilibrium between the blood and the cerebrospinal fluid. In a series of twenty-two "normal" persons they found that the average amount of sugar in the blood was 98 mg. per hundred cubic centimeters, and in the spinal fluid 65 mg. per hundred cubic centimeters. These figures yield an average ratio of distribution of 1.51. The average of the ratios obtained by us was 1.5. Hence it can be said that the group as a whole showed a normal distribution of sugar between the two fluids. Nevertheless, the individual determinations varied considerably. In the present state of knowledge it is impossible to attach any significance to these variations. They did not occur with any regularity in the different types of alcoholic psychosis. There was no apparent relation between the ratios of distribution of sugar, calcium and bromide.

The ratio of distribution of chlorides was estimated for thirteen patients (table 5). According to Leipold,[16] the normal range is from 0.78 to 0.85. All our figures were within these limits, in spite of the fact that low absolute values were occasionally obtained. As sodium bromide was administered to these patients, it should be remembered that the method used for the determinations of chloride really measured the total amount of halogens. It was apparent that the halogen content of the blood was accurately reflected in the spinal fluid, regardless of the behavior in this respect of the other substances investigated by us.

EFFECT OF ALCOHOL ON THE DISTRIBUTION RATIO OF BROMIDE IN SCHIZOPHRENIA

In order to determine the effect of alcohol on the ratio of distribution of bromide in other psychoses, our records were examined for observations made on schizophrenic patients who were intemperate. This group was chosen because it was the only one containing enough material to be of any value. Even here, however, we were able to find records of only fourteen patients in whom other complications were absent and by whom alcohol had been used to excess within a short

15. Fremont-Smith, F.; Dailey, M. E.; Merritt, H. H.; Carroll, M. P., and Thomas, G. W.: The Equilibrium Between Cerebrospinal Fluid and Blood Plasma: I. The Composition of the Human Cerebrospinal Fluid and Blood Plasma, Arch. Neurol. & Psychiat. **25**:1271 (June) 1931.

16. Leipold, W.: Durchlässigkeitsverhältnisse der Blutliquorschranke, Inaug. Diss., Greifswald, 1928.

time previous to the date of admission. Most of these patients were regarded as chronic drinkers. In an earlier communication [2b] it was demonstrated that the ratio of distribution of bromide was above 3.2 in 60 per cent of the patients with schizophrenia. In 38 per cent it was between 2.8 and 3.2, and in 2 per cent it was below 2.8. These figures differ greatly from those obtained in the cases complicated by alcoholism. A glance at table 6, in which the data are arranged, shows that more than half of the original ratios were low. Only one patient exhibited an initial ratio above 3.2. The later determinations regularly yielded higher values than the earlier ones. Although the number of

TABLE 6.—*Distribution Ratio of Bromide in Schizophrenia Complicated by Alcoholism*

Patient	Age	Date of Admission	Date of Lumbar Puncture	Distribution Ratio of Bromide	Diagnosis
J. R.	40	1/27/30	2/ 6/30 8/13/31	2.10 2.78	Schizophrenia (catatonic)
D. M.	60	5/19/28	6/21/28 1/16/30 2/13/31	2.17 2.40 3.56	Schizophrenia (paranoid)
C. L.	44	11/23/28	12/ 6/28	2.37	Schizophrenia (paranoid)
H. M.	24	4/23/29	5/ 3/29	2.49	Schizophrenia (catatonic)
T. S.	32	2/ 2/28	2/16/28 1/16/30	2.51 3.10	Schizophrenia (paranoid)
J. D.	44	6/29/31	8/12/31 12/ 9/31	2.62 2.86	Schizophrenia (paranoid)
C. M.	26	8/28/28	10/11/28 12/ 5/29	2.64 2.92	Schizophrenia (hebephrenic)
J. F.	28	3/ 2/29	3/14/29 12/12/29	2.68 3.15	Schizophrenia (catatonic)
E. M.	53	7/11/31	7/29/31	2.91	Schizophrenia (paranoid)
E. E.	34	3/ 2/27	4/18/27	3.02	Schizophrenia (catatonic)
J. B.	43	5/ 3/28	7/ 5/28	3.07	Schizophrenia (paranoid)
W. M.	51	12/22/27	1/ 5/28	3.13	Schizophrenia (paranoid)
J. C.	24	2/ 4/30	2/27/30	3.18	Schizophrenia (catatonic)
H. R.	39	2/25/29	3/ 7/29	3.60	Schizophrenia (paranoid)

observations was not large, the results were uniform enough to suggest strongly that alcohol lowers the ratio of distribution of bromide in persons with schizophrenia. It is perhaps of interest to note that at the onset of the psychosis many of these patients presented mental symptoms which resembled the clinical picture of alcoholic hallucinosis. In all instances, however, the clinical course and final development of the disorder were typical of a schizophrenic psychosis.

COMMENT

Taken as a whole, our cases showed a larger proportion of low ratios for bromide and a smaller proportion of high ones than the groups studied by most other observers. The determinations made by Hauptmann [4] yielded ratios which were about equally distributed between low,

normal and high figures. Somewhat similar results were reported by von Rhodèn [6] and Büchler.[8] Walter [5] obtained normal values in the majority of his cases. Low ratios did not occur in them. Our figures resemble those of Gordy and Smith,[7] who found low ratios in half of their group. None of their cases exhibited high values for bromide.

An analysis of our data suggests that the excessive use of alcohol tends to lead to a temporary increase in the proportion of bromide in the spinal fluid, as measured by Walter's method. This impression was gained by a comparison of the figures obtained for different patients at varying intervals following the drinking of alcohol, as well as by the observations made in those cases in which repeated tests were performed. Although the increase was most marked in the Korsakoff group, it occurred in all types of alcoholic condition dealt with here. It was not dependent on the presence of mental symptoms at the time of investigation or on a particular type of psychosis, for the same changes were encountered in intemperate patients with schizophrenia. In fact, low ratios were found for the distribution of bromide in acutely intoxicated patients who had at no time been psychotic. These observations are in accord with the experimental work of Lokshina,[17] who showed that acute alcoholic intoxication in animals was associated with a lowering of the barrier for bromides.

It is of interest to examine our results in the light of certain views expressed by Hauptmann [4] on the pathogenesis of alcoholic psychoses. Hauptmann [4] found that patients who were intolerant to alcohol, as well as those who suffered from delirium tremens and Korsakoff's psychosis, showed an increased permeability of the blood-cerebrospinal fluid barrier, as measured by the bromide test. He advanced the theory that the disorders in question arose on the basis of this change in the barrier, as a result of which toxic substances circulating in the blood were able to come into close contact with the nerve tissue. It was thought that these substances owed their origin to impairment of the detoxicating function of the liver. It was apparent that they did not occur exclusively in delirium tremens and Korsakoff's psychosis, for similar changes of function were demonstrated by Pohlisch [18] and Büchler [19] in persons with chronic alcoholism who presented no evidence of a psychosis. In cases of this type, however, Hauptmann [4] found a normal or decreased proportion of bromide in the spinal fluid.

17. Lokshina, F. S.: The Hemato-Encephalic Barrier in Alcoholic Intoxication, Medicobiol. J. **5**:126, 1929; abstr., Arch. Neurol. & Psychiat. **26**:1323 (Dec.) 1931.

18. Pohlisch, K.: Stoffwechseluntersuchungen beim chronischen Alkoholismus, Delirium tremens und der alkoholischer Korsakow-Psychose, Monatschr. f. Psychiat. u. Neurol. **62**:211, 1926.

19. Büchler, P.: Leberstoffwechselstörungen der Gewohnheitstrinker: Beiträge zur Delirfrage, Arch. f. Psychiat. **81**:280, 1927.

Hence he assumed that an intact or "thickened" barrier would prevent the toxins from reaching the nerve cells. In his opinion, the "thickening" was due partly to constitutional factors and partly to the effect of alcohol taken over a long period of time. The fact that the resistance of the blood-cerebrospinal fluid barrier may be lowered by infections or cerebral traumas was put forward by Hauptmann [4] to explain the frequent association of such conditions with attacks of delirium tremens and Korsakoff's psychosis.

In some respects our observations are not in accord with these views. The evidence presented here indicates that habitual drinkers may show low ratios for the distribution of bromide and yet not develop an alcoholic psychosis. Furthermore, we were unable to find any correlation between the ratio of distribution of bromide and the ability to withstand the ordinary effects of alcohol. This is not surprising, for the type of intolerance exhibited by persons who easily become intoxicated is generally attributed to the direct action of the alcohol itself, which is very freely diffusible in the body. Hence, as Walter [5] pointed out, one would hardly expect changes in the barrier to have any appreciable influence on the distribution of this substance between the blood and the cerebrospinal fluid.

On the other hand, there were certain features which might seem to lend support to Hauptmann's [4] theories concerning the protective function of the blood-cerebrospinal fluid barrier in alcoholic conditions. Thus, patients with delirium tremens who had had numerous attacks of mental disorder showed as a group lower ratios for the distribution of bromide than patients in whom previous attacks had not occurred. Moreover, the greatest amount of damage to the nervous system was observed in patients with Korsakoff's psychosis. These patients, taken as a whole, exhibited lower ratios than the other patients investigated by us. In contrast to this, there was no evidence of permanent damage in the patients with high bromide ratios. It should be emphasized, however, that the number of cases was hardly sufficient to allow definite conclusions concerning the significance of such features.

Some of the observations of Lokshina [17] might also be regarded as favoring the views of Hauptmann.[4] Working with rabbits and guinea-pigs, Lokshina [17] found that chronic alcoholic intoxication lasting from one to three months led to a decreased permeability for bromide. When the period of intoxication was longer than six months, complete occlusion of the barrier to bromide occurred. The present investigation, however, does not suggest that chronic alcoholism in man is regularly associated with a "thickening" of the barrier. In spite of the fact that most of our patients had been habitual drinkers for many years, few of them exhibited high ratios of distribution of bromide. The question may be raised whether the discrepancy between our results and

those of Hauptmann [4] and Lokshina [17] could be due to differences in the quantity of alcohol used. The type of beverage might also be of importance, but we have been unable to arrive at a satisfactory evaluation of these factors.

In our opinion the question as to whether dysfunction of the blood-cerebrospinal fluid barrier plays a rôle in the pathogenesis of alcoholic disorders cannot be definitely answered at present. Our observations strongly suggest that alcohol tends to lower the ratio of distribution of bromide. This tendency seemed a little more marked in Korsakoff's psychosis and chronic alcoholism than in delirium tremens and alcoholic hallucinosis. In view of the fact that the various groups were too small to exclude accidental sources of error, it would not seem advisable to stress such differences. Furthermore, the exact significance of these changes is by no means clear. There was a complete lack of correlation between the ratio of distribution of calcium, sugar and chlorides on the one hand and that of bromide on the other. One might therefore be inclined to infer that Walter's method does not yield results which are representative of the condition of the barrier in a broad sense. However, it should be remembered that the ratio of distribution of some of the normal constituents of the blood may fail to show alterations in diseases which regularly lead to impairment of the function of the barrier. The figures for calcium obtained by Fremont-Smith and co-workers [20] in certain cases of meningitis illustrate this point. Hence it is possible that a damaged barrier may affect the distribution of a foreign substance, such as bromide, without preventing substances normally present in the blood and cerebrospinal fluid from maintaining their customary equilibrium.

SUMMARY

The results of a study of the blood-cerebrospinal fluid barrier by Walter's bromide method in fifty-three cases of alcoholic mental disorder are reported.

Twenty-four cases showed low initial ratios for the distribution of bromide. Values above 3.3 were obtained in five cases. The proportion of low ratios was somewhat greater in Korsakoff's psychosis and chronic alcoholism than in delirium tremens and alcoholic hallucinosis. Most of the cases with high ratios were atypical clinically.

The distribution of bromide between the blood and the cerebrospinal fluid was investigated in fourteen patients with schizophrenia who were

20. Fremont-Smith, F.; Dailey, M. E.; Merritt, H. H., and Carroll, M. P.: The Equilibrium Between Cerebrospinal Fluid and Blood Plasma: II. The Composition of the Human Cerebrospinal Fluid and Blood Plasma in Meningitis, Arch. Neurol. & Psychiat. **25**:1290 (June) 1931.

intemperate. The initial determinations yielded low ratios in eight cases and a high value in one case.

An analysis of our observations suggests that the excessive use of alcohol tends to lower the ratio of distribution of bromide, regardless of the presence of a particular type of psychosis. The same tendency occurred in patients with chronic alcoholism who had at no time been psychotic.

The ratios of distribution of calcium, sugar and chlorides between the blood and the cerebrospinal fluid were determined in a number of the patients for whom the bromide test was performed. Essentially normal results were obtained. There was no relation between the ratios of distribution of bromide, calcium, sugar and chlorides.

POLYCYTHEMIA RUBRA VERA

NEUROLOGIC COMPLICATIONS; REPORT OF FOUR CASES

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Polycythemia rubra vera is a distinct disease entity of chronic, slowly progressive type, characterized by a marked increase in the number of red blood cells and hemoglobin, cyanosis and splenic enlargement. To Vaquez belongs credit for the discovery of this entity. In this country credit is given to Sir William Osler for calling attention to the disease. Cabot had previously reported two cases, and Saundby and Russell one. The latter stated that the case of Purves Stewart's patient at Westminster Hospital was the first recognized in London.

ETIOLOGY

The fundamental etiologic factor seems to be stimulation of the hematopoietic system, without a corresponding stimulation of the organs that provide a balance by destruction of red blood cells. Therapy directed to the spleen alone causes no amelioration of symptoms or change in findings, while therapy directed to the bone marrow effects a prompt remission of variable duration. There is an overproduction of normal red cells with a certain number of immature white cells. A mere lack of oxygen does not bring this about in polycythemia rubra vera. That there is an underlying factor of similar character in several of the blood diseases has been amply proved. Christian, from the symptomatology alone, believed that polycythemia and anemia are strikingly similar. Minot and Buckman studied fifteen patients. Anemia developed in three, with "co-incident enlargement of the spleen" and a leukemic blood picture. In one of their cases the blood picture one year before death showed 15 per cent myelocytes and 15 per cent myeloblasts. Cases which began as pernicious anemia have eventually taken on the characteristics of polycythemia vera, as also have cases of leukemia, and vice versa. It would seem, therefore, that there is a common factor operating in many of the blood dyscrasias.

PATHOLOGY

The essential changes are those of overstimulation of the marrow, with hyperplasia of the erythropoietic and leukopoietic areas. The

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spleen is always enlarged. The visceral blood vessels are distended and may look like a mass of thick worms. Mesenteric thrombosis is common.

The splenic enlargement is chiefly one of engorgement, but there is also a certain amount of hyperplasia. Arteriosclerosis is common. Cerebral thrombosis, cerebral hemorrhage and softening are not uncommon. Peripheral arterial disease is frequent and accounts for the cases showing symptoms of erythromelalgia. Oppenheimer reported thrombosis of the coronary artery and thrombosis of the hepatic veins. In short, the pathology seems to be dependent on overstimulation, with overproduction, insufficient destruction and piling up of red cells, as well as a slowly moving circulation, an overfilled vascular system and a consequent vascular block.

Brown and Giffin showed conclusively that in the venous portion of the capillary loops of the nail bed there is a much greater degree of distention than in the arterial loop. This engorgement may spread to the arterial limb of the capillary, and it is probable that this gives rise to the cyanosis in many patients. The actual volume of circulating blood is usually greatly increased. The viscosity of the blood is much above normal. The rate of flow of the blood, when tested with histamine, has been shown by Brown and Giffin to be from five to ten times as slow as normal.

The basal metabolic rate is usually somewhat increased. Two of my patients showed no increase. Never is there the increase which Gunderson has stated occurs in myelogenous leukemia, in which the basal metabolic rate may be regarded as an index to the activity of the leukopoietic tissue.

GENERAL SYMPTOMATOLOGY

The disease appears most often in men between the ages of 30 and 60 years. It is also of gradual onset and rather silent, stealing up without much ado. Usually the patient is distinctly undernourished, with thin nose, thin cheeks, rather prominent malar bones and a flushed zygomatic area. The appearance is highly suggestive of a chronic toper, and unfortunately the patients may be so classified for indefinite periods. The patients complain of weakness, dizziness, vomiting, palpation, insomnia, paroxysmal attacks of dyspnea, pressure in the abdomen, fulness of the upper part of the abdomen, feeling of weight in the left hypochondrium, irritability and overreaction to excitement. Nausea unrelated to the taking of food appears often. Constipation is also present as a rule. Colicky pain and sudden severe abdominal pain are fairly common. Neuralgic pains, muscular spasm and erythromelalgia are not uncommon.

As one reviews the literature of polycythemia rubra vera, one is struck with the predominantly nervous and mental symptomatology.

This frequent involvement of the central nervous system is to be expected from the very nature of the pathologic condition. In pernicious anemia, although there is a cerebral change, which not rarely manifests itself in some type of psychosis, the overwhelming trouble is in the spinal cord in the form of subacute combined degeneration. In leukemia the trouble is more a lesion from pressure and infiltration. In polycythemia vera it is essentially vascular and primarily cerebral. This is an important difference and if kept in mind may lead to a better evaluation of the possible etiology of certain vague and indefinite, as well as some profoundly localized, cerebral symptoms. Vaquez' first patient had vertigo as in Ménière's disease, with buzzing and whistling in the ear, staggering and other symptoms. Cuffier and Sollier's patients had frequent vertigo. Osler's first recorded cases showed headache and vertigo. Osler's other three cases, among other things, presented headache, loss of vision, pains in the feet and legs, attacks of dyspnea and tortuosity of the vessels of the fundus. Cabot's patient showed sudden loss of consciousness, thick speech, collapse and spontaneous movements of the legs and feet, with weakness of the left arm and leg. This patient had a middle meningeal hemorrhage. Saundby and Russell's patient was dull and thick of speech and had a bad memory. Hutchinson and Miller's patient, in 1906, at autopsy had large soft suprarenals, injected veins, edema of the pia-arachnoid and yellow, dry softening of the tips of both occipital lobes and the tip of the temporosphenoidal lobe; the left lenticular nucleus and the right optic thalamus were red and disintegrated. In 1909, Bordochzi reported the case of a patient with chorea.

In 1912, Lucas summarized one hundred and seventy-nine cases of polycythemia vera and reported two of his own, one with a typical inflammatory choked disk identical with those seen in intracranial tumor. Three showed cerebral hemorrhage. The nervous symptoms in this group of cases varied greatly; they included tinnitus, apprehension, excitability, disturbed mentality, psychosis, insomnia, absence of knee jerks, muscular atrophy, numbness, choreiform attacks, epileptiform attacks, muscular twitchings, tremors, hemiplegia, aphasia, disturbed speech, paraphasia and loss of consciousness. In twenty-three cases in which autopsies were performed, there was softening of the brain and cord in four. As in the patient noted by McLester in 1914, itching is not uncommon and is of generalized character. Ward called attention to the headaches, which are worse when at rest and better after moderate exercise, and the throbbing and giddiness that come in attacks. One patient, while adding up figures, would suddenly lose sight of the figures and become oblivious to the surroundings, but he never fell.

In 1917, Christian summarized the neurologic findings in ten cases. He pointed out the frequent neglect of the syndrome. His patients complained of fainting, dizziness, nervousness, insomnia, disturbance of vision, headaches, scintillating scotoma, tingling in the arm and leg, wristdrop, paralysis of hemiplegic and monoplegic types, hemianopia, edema of the disks, decrease in memory, paresthesia, diplopia, blurring and other symptoms. In one case autopsy revealed bilateral thrombi in the cerebral arteries, and in another, cerebral thrombosis; still another patient was operated on for tumor, but only cerebrovascular sclerosis with softening was found. In 1922, Bassoe reported the case of a patient with brachial neuralgia, and Pollock that of a patient with paroxysmal attacks of dyspnea, which began suddenly and ended suddenly, with chorea and headache on recumbency. Owen's patient had attacks of numbness and weakness of the right arm and leg; standing still caused aching pain in the back, with tingling around the mouth; he had had migraine from the age of 19 to 35. Löwe and Popper reported a case of thrombosis of the carotid artery and cerebral arteries with encephalomalacia. Winther found mental deterioration, aphasia, apraxia and weakness of the right side, with softening in the left parietal lobe, necrotic foci in the white matter and a glial reaction; the capillaries and small blood vessels were greatly distended, with stasis and thrombosis. In 1924, LeDoux described the case of a patient with sudden dizziness who fell, but was not unconscious, and who got up and went home; subsequently he had a *left* hemiplegia and later an attack of vertigo with *right* hemiplegia.

In 1925, Bassoe called attention to the collective review by Mendel of the nervous and mental reactions in polycythemia vera; among others, he mentioned paresis, aphasia, hemianopia, apraxia, anesthesia and choreic manifestations. In 1927, Zadek reported the absence of endothelial injury in the vessels in this disease, and mentioned in the psychic sphere, excitement, exhaustion, depression, hallucinations of smell, loss of memory and compulsory ideas of obscene sexual character. Dubowy, also in 1927, reported the case of a young woman with severe headache, nausea, vomiting, paralysis of the right limbs and speech disturbance, all of which came on without loss of consciousness and cleared up rather quickly under therapy with x-rays. In 1927, Brouwer had a patient with paralysis of the right side and a speech disturbance, which had come on the year before. The patient improved considerably, and then had another attack of paralysis on the same side. At first the condition was regarded as being due to nephritis with vascular changes. The hemoglobin was 136 per cent, and the red blood cell count, 8,900,000. The etiology became, therefore, clearly established as dependent on a polycythemia. At autopsy, the brain was hyperemic, but no

well marked thrombosis was found. It was thought that the viscosity of the blood, leading to retardation of flow, had given rise to the cerebral disturbances. Brouwer also reported the case of a patient admitted for psychic disturbances, with a hemoglobin of 113 per cent and 10,620,000 red blood cells.

A series of cases at the Mayo Clinic was studied by Brockbank and reported in 1929. There were many symptoms referable to the nervous system, which were frequently not localizing. Headache was present in thirty-three of the fifty-six cases, slight mental impairment in eleven, paresthesia in eleven and general pruritus in four. Of the twelve patients of whom complete neurologic examinations were made, three had cerebrovascular accidents, five probably had visual defects, and four certainly had visual defects. Of the first four cases, left homonymous hemianopia was found in two, right partial hemiplegia in one and inferior altitudinal anopia in one. The sixth case showed an unaccountable nystagmus; the seventh was neurologically normal, and the eighth presented a complex such as in Wilson's disease. In the same year, Crosetti recorded the case of a patient with a Charcot-Marie-Tooth type of lesion and progressive Huntington's chorea who had polycythemia vera. It was also in this year that Oppenheimer reported the case of a man, aged 44, who had been operated on in 1926 for a suspected tumor of the brain. At operation, degeneration of the cortex was found. He had had tingling in the right fingers and right cheek, unsteadiness of the right hand, weakness of the right leg, stuttering, somnolence and one vomiting spell. Before operation the hemoglobin was 90 per cent, and the red blood cell count, 6,000,000. Thirteen months after operation, all the findings of polycythemia vera were present. Oppenheimer cited the case of another patient for whom a neurologist had made a diagnosis of polycythemia, but at autopsy there was a medulloblastoma of the cerebellum. Another patient, aged 30, with eight years of vertigo and salivation and attacks of blurring of vision followed by convulsion, unconsciousness and deep sleep, had a hemoglobin of 165 per cent and 11,456,000 red blood cells. In 1930, Tizianello reported the case of a man, aged 21, with spontaneous subarachnoid hemorrhage and polycythemia.

Lhermitte, in addition to other symptoms, made note particularly of patients with hemiplegia and aphasia who recovered completely. This he considered evidence of vascular slowing and not complete thrombosis. In turn, a patient exhibiting complete recovery should be investigated for the possibility of polycythemia. Lhermitte also called attention to alternating vague headache and migraine, a feeling of tension, twisting and swelling in the extremities, and to precordial pain which is more disturbing at rest. He mentioned Mendel's case of right

facial paralysis and paresthesia of the left leg, with an unaffected left upper extremity, in other words, a multiplicity of foci. He also mentioned that in the presence of a sufficiently high polyglobulia, deficiency in sustained attention, concentration of thought and memory may well be expected. Olfactory hallucinations have been described. Narcolepsy and cataplexy, hallucinations, chills and anxiety states are also observed. Lhermitte recorded the case of a man, aged 24, with typical narcolepsy and cataplexy and absence of all other findings except polyglobulia.[1] In the literature one is struck with the frequency of involvement of the right side of the body, with speech disturbance.

From a consideration of the facts cited, it appears that neurologic manifestations are the commonest symptoms in polycythemia vera. That this is true might readily be imagined when one considers the overfilling of the vessels, the backing into the arterial loops and the slowing down of the circulation. That recovery may at times be entirely complete fits in with this conception.

TREATMENT

In 1918, Eppinger and Kloss introduced the use of phenylhydrazine hydrochloride. This drug is used at present, and, together with roentgen therapy over the long bones is the most satisfactory method available.

REPORT OF CASES

CASE 1.—*History.*—M. M., a man, aged 40, who was admitted to the surgical service of Dr. Samuel Plummer at St. Luke's Hospital on May 12, 1931, had been working in one of the concessions of the Chicago Stadium. He was found lying on the floor, wringing his hands, crying and unable to talk. He was not unconscious and was not having a convulsion. He was able to walk to an automobile. When he arrived at the hospital he was apparently unconscious; he came to shortly afterward and assisted in the removal of his clothes. The reflexes on the right were increased. The abdominal reflexes were not present. The blood pressure was 128 systolic and 84 diastolic. He vomited. Following this he became rigid and cyanotic, and stertorous breathing started. The urine was normal.

Somewhat later, the wife gave the following history: The patient had been gassed in the World War. He thought that his troubles were related to the gassing. For some time past he had been having attacks of dyspnea of periodic

1. Since the original abstract of the cases to be reported appeared, Ornsteen has reported to the Philadelphia Neurological Society the case of a man, aged 40, with polycythemia, who showed numbness of three fingers of the right hand and of the ulnar part of the forearm to the elbow, some loss of power in the right hand, pain in the left temporal region, dizziness, difficulty in speech, difficulty in forming sentences and inability to sign his name or to write; he became confused while reading. The fundi showed distended, tortuous veins. The fields showed homonymous hemianopia (right, partial). The spleen was enlarged, and the hemoglobin varied from 120 to 130 per cent, with a red cell count varying from 7,800,000 to 8,900,000.

character. He had had severe headaches with much dizziness. The headaches were periodic (migraine?). There had been periodic attacks of pain, fulness and tightness across the chest, and choking spells when he was lying down. On the day of the attack described, he had been feeling well. On recovering from the initial attack and recognizing his wife, he began to cry, to pat his chest violently and to exhibit a peculiar type of breathing.

Examination and Course.—On May 13, the patient showed a central right facial weakness. He could not talk. He wrote his name on command. The blood pressure was 102 systolic and 72 diastolic. On May 14, he was still unable to talk, but was able to follow out written commands, though he did not entirely comprehend spoken words. The skin was red, with an accompanying cyanosis, especially of the face and lips. On May 15, there were unequal pupils, which responded sluggishly to light and readily in accommodation. The disks were hyperemic, but without edema or hemorrhage. The central facial weakness was still present. There was weakness of the right arm. The deep reflexes were all lively. There was mixed sensory and motor aphasia, without objective sensory findings. On May 19, the neck was stiff on movement in all directions; there were markedly positive Kernig and Brudzinski signs. Spinal puncture showed the fluid under 130 mm. of initial pressure, without block, and with much blood evenly distributed throughout the fluid. Twenty cubic centimeters of fluid was removed. On the following day, the fluid was still bloody and under increased pressure. The patient's neck was more rigid, and there were all of the usual signs of a severe meningeal irritation.

The appearance of the patient at this time was striking and called attention to the fundamental disease behind the manifestations noted. The face showed a suffused cyanosis, i. e., a cyanosis backed up with a definitely red suffusion. The lips were more cyanotic than red; the mucous membranes of the mouth, especially the palate, were fiery red: "buccal suffusion and mucosal lividity" (Osler). The redness was also manifest over the pharynx. The finger tips were cyanotic and the hands suffused. There was a pronounced gingivitis, with soft, fungated and spongy but red gums, with the usual pyorrheal line. The spleen was palpable. The liver was evidently enlarged, though rigidity made examination difficult. Photophobia was present. No pathologic changes were found in the heart, lungs, glands or abdomen, except for the spleen and liver. The neck was rigid in all directions. The Kernig and Brudzinski signs were positive. The Babinski sign and other pathologic reflexes of similar import were not observed. The pupils were very small, but reacted both to light and in accommodation. The veins of the disk were increasingly tortuous and overfilled (fundus polycythemicus of Aschner). The retina was redder than normal. The patient had motor aphasia, with some apraxia. A diagnosis was made of thrombosis of the sylvian artery, followed by a spontaneous subarachnoid hemorrhage. The cause of the thrombosis and hemorrhage was polycythemia rubra vera.

On May 23, the hemoglobin was recorded as 130 per cent; the red blood cells, 6,610,000, and the white blood cells, 10,250. On May 28, the hemoglobin was 157 per cent by the acid hematin method. The hemoglobin remained above 100 per cent and the red cells over 6,000,000 until June 15, when anemia became manifest. On June 25, the hemoglobin reached 64 per cent and the red blood cells numbered 3,270,000.

During the further course, the patient was under the care of the various members of the neurologic staff. He gradually improved. The rigidity slowly disappeared; the spinal fluid became less and less bloody; the Kernig and Brudzinski signs and the aphasia, apraxia and echolalia disappeared, and the paraphasia cleared.

On June 1, the patient was given phenylhydrazine hydrochloride, 1½ grains (0.097 Gm.), three times daily. He improved clinically, but the blood count did not at once show any change. Two weeks after starting the treatment the reduction was definite. With the reduction in the cell count and the hemoglobin, the spleen became much larger. This my associates and I believed bore out the assumption that the real seat of the trouble was in the bone marrow. When the destructive function of the spleen was activated by the use of the phenylhydrazine, it began to enlarge and did not again begin to subside until treatment with the drug was stopped. For a time cyanosis became more pronounced and the retinal veins more engorged. Mild jaundice appeared, and the van den Bergh reaction became positive (indirect). Five weeks after admission, the spinal fluid was under increased pressure and distinctly yellow.

The patient was followed in the outpatient service for a time. The anemia became apparent. He felt much better. Then he failed to attend.

On November 20, six months later, contact was again made with the patient. At this time he was asked to report for a spinal puncture because of the interest in learning whether there still was a discoloration of the spinal fluid from the previous hemorrhage. Two cubic centimeters of perfectly clear fluid, without cells, was removed without difficulty. Within twenty-four hours after this puncture the patient began to have severe pain in the back, legs and head. He became nauseated and vomited. Thirty-two hours after the puncture he had convulsions, with marked rigidity of the arms and legs and frothing of the mouth, but no involuntary movements. One convulsion lasted ten full minutes with an unconscious period for another fifteen minutes. He showed disturbing rigidity of the neck on movement in all directions, wide dilatation of the pupils, marked suffusion of the retinal field and positive Kernig and Brudzinski signs. The face was dusky; the mucous membranes were scarlet, with overlying cyanosis of the lips. The tongue was bright red. The uvula was also as red as fire. He looked like a cyanotic patient with scarlet fever. A tentative diagnosis of recurrence of subarachnoid hemorrhage was made. We were amazed, on spinal puncture, to find that the fluid contained 4,500 polymorphonuclear cells and was as cloudy and turbid as in intracellular meningitis. The spinal pressure was 180, with a final pressure of 70. No organism was cultured from the fluid. The hemoglobin was 140 per cent; the red blood cells numbered 6,360,000, and the white blood cells, 6,000. Roentgen examination showed a ring type of arteriosclerosis of the peripheral vessels. The highest fever recorded was 102 F., with the average close to 99.8 F. Six days after admission, the temperature was normal and remained so. Ten days after admission, the patient was clinically well. At this time he was transferred to the Edward Hines, Jr., Hospital, where the following data were recorded.

On Dec. 10, 1931, the hemoglobin, was 127 per cent; the red blood cells numbered 7,250,000; the white blood cells, 17,000, with 49 per cent polymorphonuclear cells, 47 per cent small mononuclear cells, 3 per cent large mononuclear cells and 2 per cent eosinophils. The nonprotein nitrogen was 36.4 mg.; the creatinine, 1.6 mg., and the sugar, 100 mg. The Wassermann reaction of the blood was negative; the Kahn reaction of the blood was 1 plus.

At the present time the patient is under treatment by x-rays to the long bones. He has had no recurrence of subarachnoid hemorrhage, but when the hemoglobin begins to rise there is a return of dizziness with vertigo and headache.

CASE 2.—*History.*—A man, aged 56, referred by Dr. Cleveland White, had had a generalized pruritus for six or seven years, without external manifestations, and his case had at times been diagnosed neurasthenia, psychasthenia, melancholia

and inferiority complex. Blood counts taken at various times, however, had shown the hemoglobin always above 100 per cent and as high as 118 per cent, with the red blood cell count varying from 4,520,000 to 6,200,000. The patient came under my observation following a massive hemorrhage from a duodenal ulcer.

Examination and Course.—The hemoglobin reading was 110 per cent, and the red blood cell count, 6,200,000. The patient was thin, with a pointed nose, suffused cyanosis of the face and dilatation of the finer veins of the face. The spleen was easily palpable. As a child the patient had noticed that just shaking the nose hard would start a hemorrhage. The leukocyte count varied between 12,000 and 35,000, with a predominant polymorphonuclear percentage and in addition from 4 to 8 per cent of eosinophils. One per cent of myelocytes was found at the first blood count, but more recently 2 per cent myelocytes had been reported. After the hemorrhage from the ulcer, the pruritus became much less. At the time of writing the patient was under treatment with benzene and x-rays to the spleen. The initial treatment with phenylhydrazine produced anemia, but did not affect the white blood cell count. Because of the percentage of myelocytes, 2 per cent, it was thought wise to administer one or two roentgen treatments over the spleen. The icterus index varied from 8 to 10. On one occasion, the blood calcium was 10 mg. per hundred cubic centimeters of blood. Because of the pruritus without external signs, the patient had been regarded as profoundly neurotic; he had been psychoanalyzed, encouraged, explained to and despaired of. The blood findings demonstrated the pathologic condition behind most of the trouble.

Case 3.—*History.*—A man, aged 38, referred by Dr. James W. Hall, complained of a feeling of apprehension, stage fright and inferiority complex; he worried easily, felt that he might break down in the midst of speaking and could not maintain a logical train of thought. This feeling never entirely passed away. The patient said that he had known for at least two years that he had too much blood.

Examination and Course.—The hemoglobin reading was 100 per cent (Sahli); the red blood cells numbered 5,640,000; the white blood cells, 6,800, with 61 per cent polymorphonuclear leukocytes. The basal metabolic rate was minus 19 per cent. The spleen was enlarged to percussion, but was not palpable. Under treatment with phenylhydrazine and small doses of thyroid, the patient improved remarkably. This I regard as a probable case of polycythemia vera.

The patient was lost sight of for some time. On Dec. 8, 1932, he returned, stating that he had been suffering from insomnia for a few days, had felt well until lately, and had again noted a recurrence of apprehension, a feeling of not being equal to the occasion and of "feeling for words." The hemoglobin was recorded on this date as 102 per cent (Sahli units) and 124 (Hellige) per cent; the red cells numbered 5,760,000, and the white cells, 10,200; the blood pressure was 122 systolic and 76 diastolic. Treatment was again started, looking toward a reduction of the hemoglobin and cell count.

Case 4.[2]—A man, aged 41, was admitted to the hospital with a history of headaches, which came on shortly after discharge from the army in 1919. There was "itching of the fingers," and the finger tips were red. Little by little the redness increased. The patient had become nervous and could not sleep. There had been a burning, aching sensation in the feet which was aggravated by walking. During his service he carried a litter about three miles, hurrying as rapidly as

2. Dr. Torrey, of the Edward Hines, Jr., Hospital, allowed me to record this case.

possible much of the way. At the end of the journey he collapsed. Following this experience he had had headaches; his face was flushed most of the time, and he had been dizzy. After the dizzy spells one side of the face became numb; in another spell perhaps the other side, occasionally the tongue or the arm and at times the whole left side became numb. On July 21, 1932, the hemoglobin was 182 per cent (Sahli), and the red cell count was 10,420,000, with 67 per cent polymorphonuclears. Under treatment with phenylhydrazine by mouth and high voltage roentgen therapy over the long bones, the hemoglobin was reduced to 90 per cent on November 7, and the red cell count to 5,300,000.

SUMMARY

1. Polycythemia rubra vera is a clinical entity of unknown etiology characterized by a marked increase in the hemoglobin and in the number of red blood cells in the body.

2. It is of slowly progressive character, always associated with splenic enlargement, and characteristically manifests itself in suffused cyanosis.

3. The symptomatology is extremely variable, but is predominantly neurologic.

4. The essential features are probably dependent on overproduction due to stimulation of the hematopoietic system, with insufficient unbalanced destruction and piling up of the increased blood supply in a slowly moving, overfilled vascular system.

5. Case 1 illustrates, in addition to the usual features of the disease, thrombosis of the sylvian artery, with paresis of the right lower part of the face and right arm and various aphasic manifestations. The patient had added thereto a spontaneous subarachnoid hemorrhage, with marked headache, nausea, vomiting, meningism, hyperesthesia and bloody spinal fluid. Later, following the disappearance of blood from the spinal fluid and immediately after spinal puncture, a sterile, pronounced, polymorphonuclear meningitis developed.

6. The second, third and fourth cases illustrate various mental manifestations observed in polycythemia vera.

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MECHANICAL FACTORS GOVERNING THE TRÖMNER REFLEX

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The digital reflex described by Trömner [1] in 1912 is generally acknowledged to be a fairly reliable sign of an organic lesion of the corresponding pyramidal pathway at some point above the sixth cervical segment of the spinal cord. The reflex is ordinarily elicited in suitable cases by suddenly flicking the terminal phalanx of the patient's middle or index finger toward his palm from a resting position of semiflexion of the wrist and fingers. The reflex response consists of a quick movement of flexion, principally at the terminal joint of the thumb and of the index finger, and less commonly at the more proximal joints also. Sometimes, in markedly spastic cases, the flexor response is seen in all the fingers of the affected side. The typical reflex is also elicited when the terminal segment of the patient's middle or index finger is pinched between the examiner's thumb and forefinger, the examiner's restraining thumb then being allowed to slip off the distal end of the patient's nail, so that an elastic rebound of the patient's finger from the position of passive flexion at its terminal joint occurs. When elicited by the latter method, the reflex is commonly called the Hoffmann sign, although Keyser's [2] careful search of the literature failed to disclose the authority for that designation. Trömner [3] evidently was using the technic of pinching or snipping the end of the patient's finger in 1913, and he failed to mention Hoffmann in connection with the method at that time.

The importance and significance of the digital reflex have been well demonstrated by the extensive studies of Fay and Gotten.[4] Keyser [2]

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Read in abstract, with demonstration of the patient, at a meeting of the Philadelphia Neurological Society, Oct. 28, 1932.

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2. Keyser, T. S.: Hoffmann's Sign or the "Digital Reflex," J. Nerv. & Ment. Dis. **44**:51 (July) 1916.

3. Trömner, E.: Ueber Sehnen-respective Muskelreflexe und die Merkmale ihrer Schwächung und Steigerung, Berl. klin. Wchnschr. **50**:1712 (Sept. 15) 1913.

4. Fay, T., and Gotten, H. B.: Some Clinical Observations on the Value of the Hoffmann Sign, Arch. Neurol. & Psychiat. **20**:1379 (Dec.) 1928.

believed that it was a primitive segmental reflex similar to defense withdrawal reactions, initiated by an irritating stimulus affecting the sensory distributions of the sixth and seventh cervical roots, with resultant contraction chiefly of those members of the flexor muscle group supplied by the corresponding cervical motor roots. So far as I am aware, no convincing evidence of the character of the necessary afferent impulses (i. e., whether corresponding to pain, to gnostic impulses or to other forms of sensation) has ever been offered. Trömner [5] believed that his reflex was analogous to the Rossolimo reflex of the toes, and that both phenomena were referred reflexes and were transmitted by the flexors; Pitfield [6] assumed that the digital reflex was a form of tendon reflex excited by a stimulus acting through the extensor tendons; but neither of these authors offered any clinical observations directly supporting their respective interpretations.

An unusual opportunity for studying the nature of the phenomenon has been afforded me by the coexistence in one patient of a lesion of the central nervous system, undoubtedly capable of causing a Trömner reflex response in each hand, and of an isolated lesion of a tendon of the flexor digitorum profundus muscle just proximal to the terminal segment of the middle finger of the left side, effectively preventing the transmission of mechanical stimuli by way of that part of the tendon, yet in no way blocking the transmission of impulses not dependent on the integrity of the tendon.

REPORT OF A CASE

I. F., a man, 43 years of age, was a patient in the service of Dr. William G. Spiller at the Hospital of the University of Pennsylvania. He presented evidence of a lesion involving the pyramidal tracts on each side in the upper cervical part of the spinal cord. He had great exaggeration of the tendon reflexes of all four extremities, bilateral ankle and patellar clonus, bilateral Babinski reflex, grave loss of gnostic sensations in all four limbs and mild disturbances of vital sensations. The Queckenstedt test showed a block of the circulation of the cerebrospinal fluid. The signs undoubtedly indicated interruptions of the pyramidal tracts, among others, in the upper cervical part of the spinal cord, probably as the result of a tumor or arachnoiditis at the fourth cervical segment.

Of particular interest was the presence of a distinct digital reflex on the right side, elicited by the Trömner method of flicking or snapping the terminal phalanx of the middle finger. Similar digital reflex responses were obtained in this patient by the same sort of manipulation of any of the digits of the right hand, including the little finger and the thumb. On the left side, however, no response was obtained by such stimulation through the agency of the middle finger, although by using any other digit of the left hand the responses were prompt and quite comparable to the responses to stimulation of the corresponding fingers of the right hand.

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5. Trömner (footnotes 1 and 3).

6. Pitfield, R. L.: The Hoffmann Reflex: A Simple Way of Reinforcing It and Other Reflexes, J. Nerv. & Ment. Dis. **69**:252 (March) 1929.

The explanation of the lack of response through the middle finger of the left hand probably lies in the fact that the tendon of the flexor digitorum profundus muscle near the base of the distal phalanx had been severed or injured to such an extent that the voluntary action of that muscle in flexing the distal joint of the middle finger was lost. The patient, years ago, sustained an injury which crushed and lacerated the soft tissues of the distal segment of the finger, and although there was little visible deformity of the part, and no limitation of passive movement of the joint, the patient stated that since the time of that injury he had been unable voluntarily to flex the last joint. Careful testing of the individual movements of all the fingers of the hand showed no other abnormalities, aside from the general spasticity and ataxia which were evidenced in all movements of the limbs. There was no marked interference with flexion at the metacarpophalangeal and the proximal phalangeal joints, and all voluntary movements of extension of the fingers had about normal power.

Because of its deep position, no isolated contraction of the left flexor digitorum profundus muscle could be obtained by electrical stimulation, but moderate stimulation of its motor point caused flexion at all joints of the fingers, except the distal joint of the middle finger. If that finger was forcibly held in hyperextension at the metacarpophalangeal joint and in full extension at the proximal phalangeal joint, the distal joint remaining free, then, and then only, could a strong tetanizing faradic current produce some flexion at the distal phalangeal joint. Even when the finger was held in the same position, i. e., in a position which as nearly as possible neutralized any slack of the tendon of the deep flexor, no voluntary flexion at the distal joint was possible. Evidently, therefore, in order to produce such movement, the flexor muscles were made to contract more powerfully and in greater extent than was possible by voluntary innervation. From this it may be inferred that such part of the deep flexor tendon as remained attached to the base of the terminal phalanx of the middle finger was streched and relaxed to such a degree that only an unusual shortening of the muscle in contraction was capable of effecting a movement at the distal joint. By the same token, it may be assumed that a natural position of partial flexion, or even a full extension of the finger, did not put tension on the flexor digitorum profundus and its tendon. Obviously, therefore, permitting the distal segment to rebound from a position of flexion, as is done in testing the digital reflex, did not subject the flexor muscle or its tendon to a sudden stretching force of much consequence. If, however, the method of reenforcement of Pitfield [6] was applied, the digital reflex then became positive, although it readily became exhausted after from four to six trials.

Testing the reflex by a modified technic, especially devised to subject the tendon of the flexor digitorum sublimis in this case to a sudden stretching "impact," a response of moderate amplitude, apparently identical in nature with the usual positive digital reflex, was obtained without reenforcement. The modified test was made by holding the patient's middle finger in a position of hyperextension at the metacarpophalangeal joint, and in strong flexion at the proximal phalangeal joint, then, by slipping the restraining hold off the middle segment of the finger, permitting a sudden rebound from the position of forced passive flexion at the intermediate joint. Such a procedure, imparting a sudden stretching force to the tendon of the flexor digitorum sublimis, resulted in the moderate response mentioned.

Other procedures which impart a sudden stretching impulse to a tendon of the deep flexor muscle, such as percussing the volar surface of the distal phalanx of any digit other than the left middle finger, or otherwise suddenly causing extension of the last joint, produced a reflex contraction of the flexors of the finger and thumb in all respects similar to the Trömner response.

COMMENT

A study of this patient seems to demonstrate, so far as this particular case is concerned, the necessity of imparting an adequate and sudden stretching "impact" to the flexor digitorum profundus muscle, the flexor digitorum sublimis, the flexor pollicis longus or a tendon of one of these muscles if the digital reflex response is to be obtained. A careful analysis of the mechanical effect of the flicking or snapping of the distal phalangeal segment, as is usually done in testing for the reflex, shows that by either technic there is effected a forced passive flexion at the distal joint, followed by a sudden release from such forced flexion, resulting in a rebound from flexion and therefore a stretching of the flexor tendons. This suggests that the phenomenon may be the response to stretching the flexor muscles or their tendons when a state of abnormally increased muscle tonus or abnormally lowered resistance of the threshold of reflex excitability exists. A further indication of the probability that it is a tendon reflex rather than purely a defense withdrawal effect in this case is the fact that percussing the volar surface of the terminal phalanx of a partially extended finger (other than the left middle finger) resulted in a flexor response identical with the typical Trömner response, whereas percussing the dorsal surface of the same segment produced no response. The former act imparts a stretching force to the deep flexor tendon; the latter affects the extensor tendon in a similar way, and both acts afford similar local irritation within the same cutaneous segmental sensory zone.

CONCLUSION

Although no far-reaching conclusions should be drawn on the basis of observations in a single opportune case, the studies in this instance seem at least to favor the classification of the digital reflex among the tendon reflexes, probably operative through the sensory and motor fibers connected with the flexor digitorum profundus, flexor digitorum sublimis and flexor pollicis longus muscles or their tendons.

Clinical Notes

USE OF SODIUM AMYTAL IN PREVENTION OF REACTIONS ASSOCIATED WITH LUMBAR PUNCTURE

GEORGE V. KULCHAR, M.D., AND ALLEN D. KING, M.D., PHILADELPHIA

In the decades that have lapsed since its introduction by Quincke,[1] lumbar puncture has passed from the realm of surgery into that of diagnostic medicine and therapeutics. Yet, despite simplification and many refinements of technic, reactions following lumbar puncture, even when the operation is performed by an expert physician, are frequent and distressing. According to Stokes,[2] when every precaution is used, some degree of reaction occurs in from 15 to 25 per cent of patients when they arise from bed on the day following puncture. Under similar conditions, Nelson [3] reported the incidence of reactions as being about 20 per cent. In a small series, Alpers [4] found the incidence of headaches following puncture to be about 17.5 per cent. In 852 patients, Perkel [5] noted signs of meningism in 37.7 per cent, appearing from one to ten days after puncture. While reactions may be expected in from 17.5 to 37.7 per cent of patients hospitalized immediately following lumbar puncture, they must occur with greater frequency in ambulatory patients. No report of the incidence of reactions in the latter has come to our attention.

Various procedures have been suggested to prevent or relieve headache following lumbar puncture. By means of an ingenious device, Nelson inserted catgut into the dural wound in an attempt to avoid leakage. Sicard,[6] Frenkel [7] and others advised confining the patient to bed with the head lowered for from twenty-

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The sodium amytal used in this study was supplied by Eli Lilly & Co.

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2. Stokes, J. H.: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1928, p. 201.

3. Nelson, M. O.: Postpuncture Headaches, Arch. Dermat. & Syph. **21**:615 (April) 1930.

4. Alpers, B. J.: Lumbar Puncture Headache, Arch. Neurol. & Psychiat. **14**:806 (Dec.) 1925.

5. Perkel, J. D.: Contribution à l'étude des accidents secondaires qui suivent la ponction lombaire, Presse méd. **33**:1320, 1925.

6. Sicard, J.: Le liquide céphalorachidien, Paris, Masson & Cie, 1902.

7. Frenkel, H. S.: Zur Zytodiagnose des Liquor cerebrospinalis, Neurol. Centralbl. **22**:610, 1903.

four to forty-eight hours after puncture. The importance of keeping the patient quiet while he is in bed was emphasized by Gennerich [8] and by Eichelberg and Pförtner.[9]

In an attempt to overcome the low pressure of the cerebrospinal fluid during headaches, resulting from lumbar puncture, Jacobaeus and Frumerie [10] injected physiologic solution of sodium chloride intraspinally with some success. Solomon,[11] Perkel and Alpers found the subcutaneous injection of solution of pituitary or the intravenous administration of hypotonic solutions to be of considerable value in the relief of reactions following puncture. Though these measures were first used empirically, further studies have indicated that they have a common pharmacologic basis. Becht and Gunnar [12] demonstrated experimentally that the rise in cerebrospinal fluid pressure following the administration of pituitary is due to the displacement of preformed spinal fluid, owing to the increased venous pressure. There is no apparent increase in the production of spinal fluid. A prolonged increase in the spinal fluid pressure was demonstrated by Weed and Hughson [13] following the intravenous injection of hypotonic solutions. These investigators showed the increase to be in part dependent on the accompanying rise in the cerebral venous pressure. The changes in the osmotic pressure of the blood, with the consequent compensatory readjustment of fluids in the tissues, according to Weed and McKibben,[14] explain the rise in cerebrospinal fluid pressure following the intravenous injection of hypotonic solutions.

The peculiarly adaptable pharmacologic properties of sodium amytal (sodium iso-amylethylbarbiturate) suggest that it may be of considerable value in the prevention of reactions following lumbar puncture. Emge and Hoffman [15] noted that the maximum sedative action of sodium amytal appears in from five to ten minutes following its oral administration. This pronounced sedative effect passes off more slowly than the narcosis secured with other commonly used preparations.

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8. Gennerich, W.: Die Syphilis des Zentralnervensystems; ihre Ursachen und Behandlung, Berlin, Julius Springer, 1921.

9. Eichelberg and Pförtner: Die praktische Verwertbarkeit der verschiedenen Untersuchungsmethoden des Liquor cerebrospinalis, Monatschr. f. Psychiat. u. Neurol. **25**:485, 1909.

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11. Solomon, H. C.: Raising Cerebrospinal Fluid Pressure with Especial Reference to the Effect on Lumbar Puncture Headache, J. A. M. A. **82**:1512 (May 10) 1924.

12. Becht, F. E., and Gunnar, H.: A Study of the Volume Changes of the Cerebrospinal Fluid after Adrenalin, Pituitrin, Pilocarpine and Atropine, Am. J. Physiol. **56**:231, 1921.

13. Weed, L. H., and Hughson, W.: Systemic Effects of Intravenous Injection of Solutions of Various Concentrations with Special Reference to the Cerebrospinal Fluid, Am. J. Physiol. **58**:53, 1921.

14. Weed, L. H., and McKibben, P. S.: Pressure Changes in the Cerebrospinal Fluid Following Intravenous Injection of Solutions of Various Concentrations, Am. J. Physiol. **48**:512, 1919.

15. Emge, L. A., and Hoffman, P. E.: Clinical Observations on the Relation of Sodium Amytal to Vasomotor and Diuretic Phenomena after Oral Administration, Am. J. Surg. **9**:16, 1930.

Garry [16] stated that the sedative action persists for from twelve to seventy-two hours. Owing to the freedom from nausea, patients receiving sodium amytal are able to take more fluids. At the same time there occurs inhibition of water diuresis, as noted by Garry, Emge and Hoffman, and others. Ogden [17] showed experimentally that this inhibition of the elimination of excess water is immediate and complete, and that it persists for more than ten hours. While the physiologic mechanism of the oliguria observed following the administration of sodium amytal requires further investigation, Bourne, Bruger and Dreyer [18] demonstrated that it is accompanied by hydremia. This, they suggested, may be due to a change in the salt constituents of the blood and does not necessarily imply an increase in the blood volume. The change in the salt content which reflects itself in the osmotic pressure is interesting, as the work of Weed and his associates showed this to be the physiologic mechanism of the increase in the spinal fluid tension following the administration of hypotonic solutions intravenously. Pituitary, long advocated in the treatment of headache following lumbar puncture, likewise favors retention of water through inhibition of diuresis. The forced increase in the intake of fluids which has been advised as a routine following lumbar puncture may serve to increase the hydremia in patients in whom water diuresis has been inhibited. A common physiologic mechanism, namely, a change in the osmotic pressure of the blood, may thus in part underlie the methods usually employed in the treatment of reactions resulting from lumbar puncture.

In an effort to determine clinically whether sodium amytal is of value in the prevention of the reactions following lumbar puncture, a study was made on ambulatory patients subjected to lumbar puncture under carefully controlled conditions. In 199 consecutive lumbar punctures done under uniform conditions, variations were made only in the amount of cerebrospinal fluid withdrawn and in the time required for the operation, in order to study the possible relation of these factors to the incidence of reactions. Four platinum-iridium needles of the Bier hub type, uniform in caliber (19 gage), with bevel points, were used for the entire series. Each patient was instructed to take a light breakfast two hours before coming to the clinic. If a sedative was to be administered before puncture, either 3 grains (0.18 Gm.) of sodium amytal was given by mouth or ½ grain (0.03 Gm.) of codeine was given hypodermically. The patient was then instructed to lie quietly in a darkened room for thirty minutes before the puncture was done. In all instances, except a few in which a second attempt was necessary, the puncture was made through the fourth lumbar space. The pressure of the cerebrospinal fluid before and after the withdrawal of the fluid, the amount of fluid withdrawn and the time required for the withdrawal were noted. Following puncture the patient was kept on the table in the prone position for one hour. On being permitted to go home, he was instructed to increase the intake of fluids as much as possible and to remain flat in bed for twenty-four hours.

The most common type of reaction observed was severe throbbing headache in the occipital and frontal regions, beginning from eighteen to twenty-four hours

16. Garry, R. C.: Pharmacological Properties of Iso-Amyl Ethyl Barbituric Acid (Amytal), Brit. M. J. **1**:421 (March 5) 1932.

17. Ogden, E.: Inhibition of Water Diuresis by Amytal, Proc. Soc. Exper. Biol. & Med. **27**:506, 1930.

18. Bourne, W.; Bruger, M., and Dreyer, N. B.: Effects of Sodium Amytal on Liver Function, Rate of Secretion and Composition of Urine, Reaction and Alkali Reserve and Concentration of Blood and Body Temperature, Surg., Gynec. & Obst. **51**:356, 1930.

after puncture, usually when the patient arose on the morning of the following day. In a few instances the onset of the reaction was delayed as much as forty-eight hours. As MacRobert [19] pointed out, the headache is orthostatic, coming on about twenty seconds after the patient raises his head and disappearing about twenty seconds after he lies down. Nausea and occasionally vomiting and vertigo accompanied the more severe reactions. The headache usually persisted with severity for from one to three days and then ceased somewhat abruptly. Reactions persisting for more than three days were relatively infrequent.

Of the 105 patients in this series receiving sodium amytal, the majority fell asleep while awaiting puncture. The apprehension usually manifested prior to lumbar puncture by patients in a clinic was, in most instances, absent. On the other hand, the twelve patients receiving codeine and the 82 patients receiving no sedative were, for the most part, alert and apprehensive. The mental state is further evidenced by the degree of relaxation during the operation. Of the patients receiving amytal, only 3, or 2.8 per cent, were rigid and apprehensive during puncture, while in the small series receiving codeine, 4, or 33.3 per cent, were unrelaxed and excited. Thirty-four, or 41.4 per cent, of the patients who received no sedative were rigid and apprehensive during puncture.

From the data obtained in this study, the sex of the patient, the difficulty experienced in entering the canal, the number of dural wounds made and the amount of fluid withdrawn are apparently not causal factors in the reactions following lumbar puncture. Likewise, the time required for withdrawing the fluid, the pressure of the cerebrospinal fluid immediately before and after the withdrawal and the presence of fresh blood in the fluid obtained seem to be of no etiologic importance. However, in 30 patients receiving no sedative whose cerebrospinal fluid showed evidence of syphilis of the central nervous system, the incidence of headache was 10 per cent, as compared with 25.5 per cent in a larger control series.

The typical headache caused by lumbar puncture occurred in 16, or 13.5 per cent, of the 105 patients receiving sodium amytal by mouth. Of the 12 patients who received codeine hypodermically, 4, or 33.3 per cent, showed similar reactions. Reactions occurred in 21, or 25.5 per cent, of the 82 patients who received no sedative.

SUMMARY AND COMMENT

Sodium amytal possesses distinct advantages as a sedative given before lumbar puncture. As it may be given effectively by mouth, the hypodermic injection so often objected to by the patient is avoided. The fact that the maximum sedative effect is obtained in from five to ten minutes makes it adaptable for clinical use. Much of the apprehension usually manifested by the patient prior to lumbar puncture is averted, and he approaches the operation in a somewhat drowsy, though entirely manageable, state. As he is relaxed and usually quiet on the table, puncture is made less difficult, both for the patient and for the operator. In this somnolent state the threshold for pain is perceptibly raised, the drug thus having a mild analgesic effect.

As the sedative action of sodium amytal is prolonged, the patient is more content to lie quietly in bed, even if not asleep, following puncture. Most of the patients receiving sodium amytal, however, slept during the hour in which they remained under observation. On the other hand, the patients who received codeine

19. MacRobert, R. G.: The Cause of Lumbar Puncture Headache, J. A. M. A. **70**:1350 (May 11) 1918.

or no sedative before puncture were restless, though they were cautioned to lie quiet. The sedative action of sodium amytal in most instances persisted until the morning of the following day, as revealed by subsequent inquiry. As has been stated, maintaining the patient quietly in bed following lumbar puncture favors the closing of the dural wound and decreases the amount of leakage of cerebrospinal fluid.

The reduction of the incidence of reactions following lumbar puncture from 25.5 per cent to 13.5 per cent through the use of sodium amytal may be due solely to the sedative action. The inhibition of diuresis and the hydremia which occur following the administration of sodium amytal may, however, in part account for the favorable results obtained. As has been suggested, the changes in the osmotic pressure of the blood occasioned by the hydremia result in an increase in the cerebrospinal fluid tension, compensating for the loss through leakage. It is suggested that the decrease in reactions noted is probably due to a combination of the sedative action, which favors the closure of the dural wound by keeping the patient quiet and thus decreases the amount of leakage, and the compensatory increase in cerebrospinal fluid pressure.

CONCLUSIONS

1. The incidence of reactions following lumbar puncture in ambulatory patients receiving no preliminary sedative is about 25.5 per cent.

2. The use of sodium amytal by mouth as a sedative before puncture is followed by a reduction of the incidence of reactions to 13.5 per cent.

3. Lumbar puncture is made technically less difficult for the operator and less of an ordeal for the patient if sodium amytal is given as a preliminary sedative.

STAINING OF OLIGODENDROGLIA AND MICROGLIA IN CELLOIDIN SECTIONS

ARTHUR WEIL, M.D., AND HAROLD A. DAVENPORT, M.D., CHICAGO

The ideal technic for staining nerve tissue would allow one to stain by specific methods all the different structures in serial sections from one and the same block of embedded tissue. A step forward toward the accomplishment of this goal has been the method devised by Stern[1] for the staining of microglia and oligodendroglia in celloidin sections. As indicated by his photomicrographs, the method gives excellent results, especially in cases of pathologic glial proliferation. We were able to confirm his results by following exactly his directions.

Even trained technicians, however, do not always succeed in the preparation of the silver solution devised by Stern, and, besides, the use of a 10 per cent commercial formaldehyde solution in connection with 10 per cent ammoniacal silver nitrate frequently leads to the production of disturbing silver precipitates (Kubie).[2] Therefore, we have modified the method somewhat in order to make it useful for routine laboratory work.

In both modifications, oligodendroglia as well as microglia are impregnated. For routine laboratory work either method may be used; we prefer the first method for microglia, because it is easier to avoid the formation of disturbing precipitates. The time of staining in the ammoniacal silver nitrate has to be determined empirically for the different tissues.

METHODS

Staining of Microglia.—1. Wash a pyroxilin (celloidin) section, 15 microns thick, in distilled water.

2. Stain sections for from ten to twenty seconds in a solution made as follows: To 2 cc. of concentrated ammonia water add a 10 per cent solution of silver nitrate drop by drop from a buret (approximately 18 cc.), shaking the solution in order to prevent the formation of a precipitate. The end-point of the titration is a slight opalescence of the solution. If through an excess of silver nitrate a precipitate has been formed, or if in the formaldehyde solution a heavy precipitate forms on the section, a drop of concentrated ammonia is added, and again the mixture is titrated with a 10 per cent solution of silver nitrate to the correct point, i. e., the first appearance of a slight opalescence.

From the Institute of Neurology and the Department of Anatomy, Northwestern University Medical School.

1. Stern, J. B.: Ztschr. f. d. ges. Neurol. u. Psychiat. **138**:769, 1932.

2. Kubie, L. S.: Staining of Tissues of the Central Nervous System with Silver, Arch. Neurol. & Psychiat. **22**:135 (July) 1929.

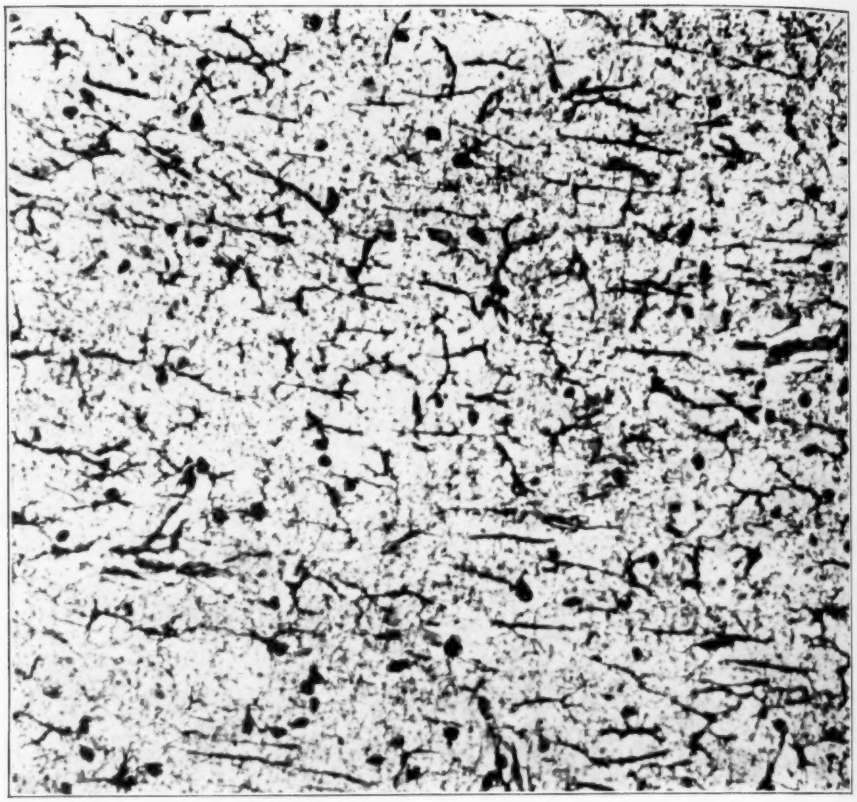

Fig. 1.—Frontal cortex in case of dementia paralytica stained for microglia. Leitz obj., 10; ocul., × 10; linear magnification, × 170.

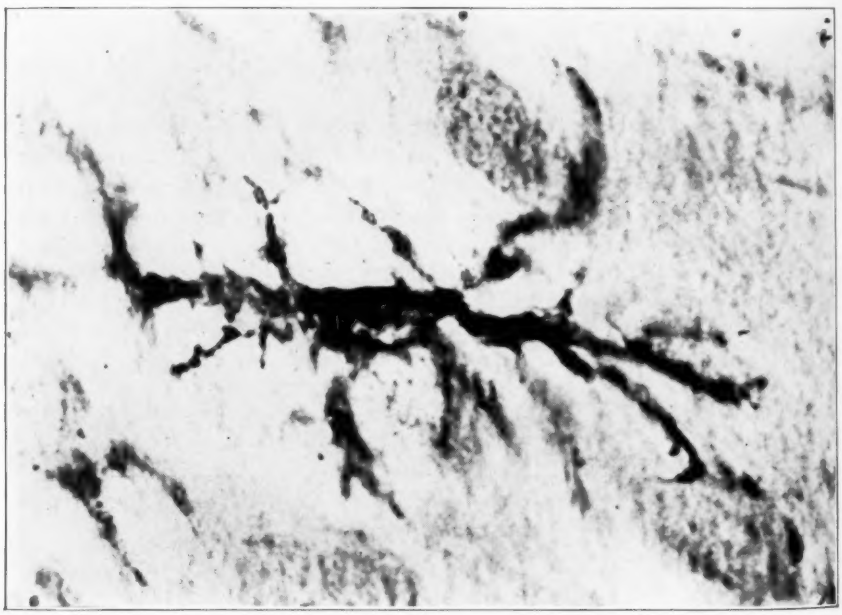

Fig. 2.—Microglia (rod cell). Beck obj.; 2 mm. ap.; ocul. × 10; linear magnification, × 1,800.

Sometimes staining of the microglia cannot be obtained with solutions at this first stage of opalescence. On the addition of another drop of silver nitrate and the extension of the time of staining to fifteen seconds, better results may be obtained. It is essential to avoid the formation of a precipitate.

3. Transfer the section to a solution of formaldehyde (prepared by diluting one part solution of formaldehyde, U. S. P., with water to make six parts), moving it rapidly until a coffee-brown color has been produced. The formaldehyde should be renewed for each section.

4. Transfer through three changes of distilled water.

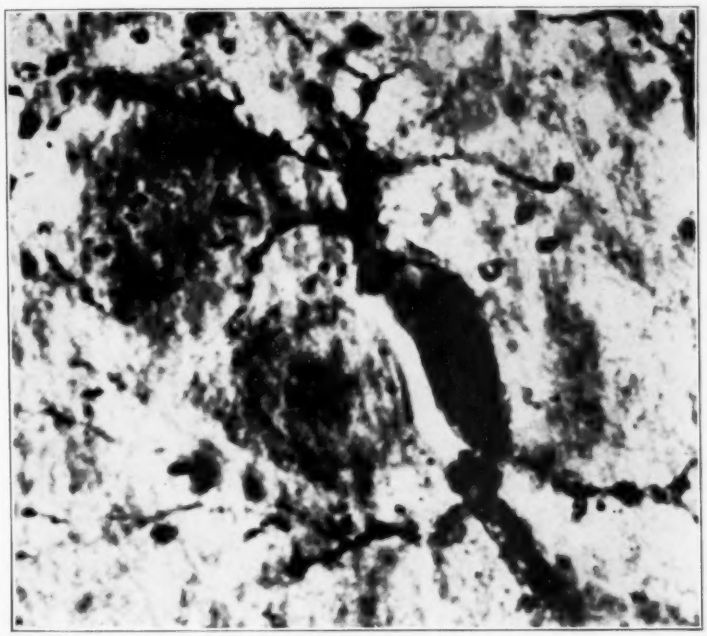

Fig. 3.—Frontal cortex in case of arteriosclerosis stained for microglia, showing satellite surrounding ganglion cells. The objective and magnification are the same as in figure 2.

5. Dehydrate in alcohol, clear in xylene and mount in balsam. The sections should be mounted immediately because keeping them in xylene results in fading.

Staining of Oligodendroglia.—1. Wash sections in distilled water and transfer to water containing a drop of concentrated ammonia per ten cubic centimeters.

2. Stain sections for from fifteen to twenty seconds in silver solution which has been prepared as already described, the only exception being that a 15 per cent solution of silver nitrate should be used. Approximately 12 cc. of it will have to be added to 2 cc. of concentrated ammonia until the end-point of the titration has been reached.

3. Transfer to solution of formaldehyde (prepared by diluting one part solution of formaldehyde, U. S. P., with water to make ten parts) and allow the section to drop to the bottom of the dish, without moving it. After the pyroxilin is darkly stained and the tissue begins to take a brown color, move it with a glass rod until it is stained coffee-brown. Use fresh formaldehyde for each section.

4 and 5. The fourth and fifth steps are the same as those employed in the staining of microglia.

Obituary

HENRY GEORGE MEHRTENS
1884-1933

In the midst of a career replete with academic and scientific successes, Henry George Mehrtens died of coronary occlusion on Feb. 28, 1933, after an illness of two weeks.

He was born on Nov. 15, 1884; he graduated from the University of California with the degree of Bachelor of Science in 1911, and as Doctor of Medicine from Stanford University Medical School in 1914. From that time forward he was connected with the Stanford Medical School successively as instructor, assistant professor, associate professor and professor of medicine in the department of neuropsychiatry. He had been acting dean of the Medical School since June, 1932.

Soon after receiving the doctor's degree, he came into intimate contact with Dr. A. W. Hoisholt, then superintendent at the Napa State Hospital. His interest immediately gravitated to the study of human behavior and psychiatry. No less an influence in his early career was the friendship and guidance given him by Ray Lyman Wilbur, then dean and professor of medicine at the Stanford Medical School.

In 1924, he became a member of the American Neurological Association; in 1925, a Fellow of the American Psychiatric Association, and in 1931, a Fellow of the American College of Physicians.

Dr. Mehrtens was a man of wide interest, known not only as a physician and teacher, but also as a research worker and medical administrator. His interest led him into the field of classical literature, for which pursuit he possessed a very complete library. In this connection he was known as a collector of Stevensoniana, his collection comprising many choice volumes, manuscripts and personal mementos of this author; this was his hobby.

In 1924, he married Helen Clare Kent, who by sympathetic, intelligent and truly spiritual interest aided him, no doubt, in his very successful career.

Among his contributions in his own special sphere, the work for which he is best known are his publications on the treatment of syphilis of the central nervous system and the working out and application of iodobismitol in the treatment of syphilis.

From the first he showed that he possessed great capacities as an organizer, leader and counselor of men, and the qualities of a great physician. He considered medical problems in his own research and in that of persons who worked with him from the outlook of a trained, scientific mind.

He will be hard to replace in the Medical School; his many patients and his friends will miss his delightful human sympathy and his wide understanding.

JULIAN M. WOLFSOHN, M.D.

Abstracts from Current Literature

THE VEGETATIVE PORTION OF THE SPINAL CORD. O. GAGEL, Ztschr. f. d. ges. Neurol. u. Psychiat. **138**:263 (Jan.) 1932.

One of the most important problems relating to the vegetative nervous system has to do with the efferent and afferent paths of this system.

Efferent Path.—Foerster furnished physiologic proof of the existence of vegetative conduction paths in the anterior roots by means of the sweat and pilomotor reactions. He was able to produce secretion of sweat by stimulation of an anterior thoracic root in an area covering several dermatomes. This confirmed the work of Diedens who deafferented a hind limb of a dog, and found on stimulation of the lumbar cord that secretion of sweat took place in this leg. He concluded, therefore, that these fibers run in the anterior roots. Foerster, by stimulation of a single anterior thoracic or lumbar root, produced a pilomotor reaction in several dermatomes. Similarly, Foerster showed that in the anterior roots of the eighth cervical and first and second dorsal nerves there are efferent fibers for the dilator pupillae. Vasoconstrictor fibers have been demonstrated by Pflüger. They were proved to exist in man by Foerster and Altenburger, who found a definite vasoconstriction by plethysmograph on stimulation of the peripheral ends of the severed anterior roots of the third and fourth dorsal nerves. Latterly, Gagel was able to demonstrate degeneration in the lateral horns of the spinal cord in a patient in whom the anterior roots of the third and fourth dorsal nerves had been cut. Since these lateral horns are connected with the vegetative nervous system, it is presumed that efferent tracts run through the anterior roots.

Efferent vegetative fibers have been found also in the posterior roots. Proof of this was given in the experiments of Bayliss and of Stricker. The latter, in 1876, found vasodilatation and an increase in temperature in the hind legs of dogs on stimulation of the distal end of the posterior roots of the sixth and seventh lumbar nerves. Foerster showed that in man such vasodilator effects can be obtained by stimulation of the posterior roots in the cervical, thoracic, lumbar and sacral regions, and that this follows a definite metameric arrangement. Bayliss explained the phenomenon as due to antidromic conduction in the dorsal roots. Finally, Ken Kuré presented anatomic evidence that on section of the posterior roots there still remain numerous undegenerated fibers in the proximal stump. This finding has been confirmed by Gagel, who studied the spinal cord in eight cases in which section of the posterior roots had been performed by Foerster. From his study of these he concluded that there are posterior root fibers which do not have their origin in the dorsal root ganglion or anywhere else outside the spinal cord, but arise within the cord itself. These efferent fibers in the dorsal root have been calculated by a pupil of Ken Kuré to be about 40 per cent of the total.

Afferent Path.—Foerster was one of the first to break away from the old concept that only the posterior roots mediate afferent vegetative stimuli. He observed that patients in whom section of the posterior roots has been performed experienced relief from pain only transitorily, and that sensation was not completely absent. Further, he found that stimulation of the central stump of a sectioned anterior root caused pain. He believed that a part of the body was deafferented only when the posterior and anterior roots were cut, looking on the latter as an auxiliary pathway for the posterior roots. Anatomic proof of the presence of afferent fibers in the anterior roots is still lacking. Attempts have been made to trace Marchi degeneration in the anterior roots after removal of a sympathetic ganglion. Nottebaum found no degeneration after section of the cervical sympathetic ganglion. Truschkowsky extirpated the abdominal ganglion of the sympathetic nerve and found degeneration products in the anterior and

posterior parts of the cord on the same side and in the intramedullary portion of the anterior roots on the opposite side. He obtained similar results after extirpation of the superior cervical ganglion. Gagel cut the superior cervical ganglion in a young Macacus rhesus monkey and killed the animal at the end of ten days; he was unable to find products of degeneration either in the anterior or in the posterior roots. There were scattered Marchi granules in the fourth and seventh cervical roots, but they were too indefinite for one to be certain about them. Furthermore, they were bilateral. His findings disagree, therefore, with those of Truschkowsky. However, Gagel found, ganglion cells in the zone of exit of the anterior root of the sympathetic nerve in five cases. These cells, in form and arrangement, as well as in the presence of capsules, were definitely spinal ganglion cells. They speak for the presence of afferent fibers in the anterior roots. The evidence indicates that most of the afferent fibers enter the posterior roots, but there are some that enter the anterior roots.

Vegetative Centers.—Gaskell was the first to investigate the vegetative centers in the spinal cord. He found thin myelinated fibers in the anterior roots of the thoracic and upper lumbar areas. He recognized them as of vegetative origin, and thought that they came from the cells of Clarke's column. Budge produced a dilatation of the pupil by stimulation of the cord from the sixth cervical to the fourth thoracic segment in the dog, and concluded that there is a center for the pupil in this region. Biedl cut the left splanchnic nerve in dogs and was able to trace degeneration back into the anterior and lateral horns. Hoeben cut the ganglion colli supremum in rabbits and also found degeneration in the anterior and lateral horns of the cord. Herring recognized vegetative centers in the lateral horns of the spinal cord. After tearing out the paravertebral chain in dogs, Laignel-Lavastine found changes in the cells of Clarke's column, the lateral horn, the paracentral group and the zona intermedia. Lapinsky and Cassirer investigated the cord in seven rabbits in which the superior and inferior cervical ganglia had been extirpated. Their results were negative, and they called attention to the difficulty of demonstrating changes in the small ganglion cells. Recently, Kai resected the sympathetic chain in dogs which he killed at varying intervals. He found acute and chronic changes in the cells in the the zona intermedia in the cervical cord, in the lateral horn cells of the thoracic and lumbar cords and in the sacral cord in the transition zone between the anterior and posterior horns. Foerster extirpated the superior cervical ganglion in a monkey, which was killed ten days later. Pathologic changes were found in the lateral horns of the first, second and third thoracic segments, and only on the side operated on. These changes consisted in a shrinkage of the lateral horn cells as compared with those of the normal side, and also in a definite decrease in the number of these cells. There were no visible changes in the cells of the anterior horn or of Clarke's column. Further evidence of the vegetative nature of the lateral horn cells has been brought forward by Bok, who was able to follow the neurites of the lateral horn cells in guinea-pig embryos through the tractus lateroventralis to the anterior roots. These fibers were more finely myelinated than the anterior root fibers, and Bok looked on them as sympathetic. The origin of the afferent fibers in the posterior horns has been worked out by Ken Kuré, who found that they come from small ganglion cells which lie between the anterior horns and the substantia gelatinosa. Gagel studied this problem, using a patient in whom a posterior and two anterior roots had been cut and two monkeys with transected posterior roots. In man no changes were found. In the monkey he found a decrease in the number of ganglion cells in the zona intermedia, without changes in the cells, which is a questionable finding at best.

Vasomotor Centers.—Goltz and Ewald (1896) observed in vertebrates and in invertebrates that vascular paralysis occurred in the caudal portion of the body after section of the cervical cord. The decreased vascular tonus returned slowly to normal, and a new loss of tone was observed only after section of the thoracic cord. It seems, therefore, as if there is a vasomotor center there. Langley found that the blood pressure can be increased in cats with cords transected at the

cervical level by stimulating the central end of a nerve such as the sciatic. Schlesinger obtained similar results in strychninized animals. Stricker observed vasodilatation in the hind leg after stimulation of the distal end of the sixth and seventh lumbar roots. These observations suggested the presence of vasodilator fibers in the posterior roots. Bayliss and Langley confirmed these observations in cats and dogs. Foerster has observed many times in man that stimulation of the distal end of a severed posterior root causes vasodilatation. This vasodilatation has a metameric distribution. The cells in the intermediary zone are probably the centers for the vasodilator fibers. It is probable that the vasoconstrictor center lies in the lateral group of cells.

Pilomotor Centers.—Foerster showed that on stimulation of an anterior root in the thoracic or lumbar cord there followed a definite pilomotor reaction over several dermatomes. This indicated that a single anterior root gives off preganglionic fibers to several ganglia of the prevertebral chain. Pilomotor erection can be elicited over the entire segment body, including the head, when the cord is severed at the eighth cervical segment, which indicates that the pilomotor centers for the entire body lie below this point. This coincides with the anatomic observation that the lateral horn appears first below this level. The pilomotor reaction is obtained in the lower extremities if the cord is severed at the third lumbar segment, which indicates that there are no pilomotor centers below this level. This, too, is in accord with the anatomy, as the lateral horns extend only to the second lumbar or at the very most to the third lumbar segment. The pilomotor centers, therefore, lie between the eighth cervical and the third lumbar segments. If the cord is transected at the sixth thoracic segment a pilomotor reaction is obtained from trunk to axilla, the arms escaping, since their pilomotor centers lie between the second and fifth thoracic segments.

Ciliospinal Center.—Budge placed the ciliospinal center between the sixth cervical and fourth thoracic segments. Gagel, on the basis of extirpation experiments on the superior cervical ganglion, places it in the lateral horns of the first and second thoracic segments and the oral part of the third thoracic. These observations agree with those of Foerster, who on stimulation of the anterior roots found the center for the dilator pupillae in the eighth cervical and first and second thoracic segments.

Smooth Muscles of the Trunk Organs.—Goltz and Müller determined that there is a center for erection in the lower sacral cord. After cutting the lumbar and upper sacral cord they could still obtain an erection in dogs. On the other hand, Goltz and Ewald could obtain no erection after destruction of the lumbar cord. Marburg and Ranzi were able to get erections in man with a lesion involving the whole of the cauda equina, the result of gunshot wounds. Clinical observations point to an erection center in the lower sacral cord as well as to an ejaculation center. Observations have been made on injuries to the conus with absence or decrease of ejaculation in the presence of intact erection. Foerster placed the ejaculation center oral to the erection center in the sacral cord. He observed patients with injury of the lowest part of the sacral cord in whom there was loss of erection, but intact ejaculation through the relaxed penis. On the other hand, in injuries of the first and second sacral segments there was failure of ejaculation with intact erection and function of the bladder. These observations have been confirmed experimentally by Müller.

Sweat Centers.—Foerster was the first to point out that stimulation of one anterior root caused secretion of sweat in several dermatomes. Stimulation of the fifth thoracic anterior root produced secretion in the third to ninth thoracic dermatomes. If the peripheral end of the cut posterior root of the fifth thoracic nerve was tied off, no secretion took place in this dermatome on stimulation of the anterior root, and it was less pronounced in the other dermatomes. Foerster concluded, therefore, that the posterior root carries sweat-inhibiting fibers. These observations were confirmed by Schilf. André Thomas considered the sweat centers for the head, neck and upper part of the thorax to be in the eighth cer-

vical to fourth thoracic segments; those for the arms in the fourth to seventh thoracic, and those for the legs in the ninth thoracic to second lumbar. Guttmann was able to produce reflex sweating in the lower segment of the body in a case in which the cord was severed from the seventh to tenth cervical segments. Cases of syringomyelia with involvement of the intermediary zone and lateral horns are characterized by a disturbance in secretion of sweat. Guttmann observed cases of this sort with areas of anhidrosis.

ALPERS, Philadelphia.

TRANSPORTATION OF PARTICULATE MATTER FROM THE VITREOUS INTO THE OPTIC NERVE. MILTON L. BERLINER and JOSÉ F. NONIDEZ, Arch. Ophth. **8**:695 (Nov.) 1932.

The histopathology of the retina and the optic nerve so far as phagocytosis is concerned has been in doubt, and the various reports relative to this are more or less controversial. According to Nuel and Benoit, india ink injected into the vitreous of the rabbit passes directly into the spaces around the central vessels in the optic nerve. The observations of Berlinger and Nonidez are definitely opposed to this. They agree with Evans, who had repeated the experiments of Nuel and Benoit. It is likely that the two latter used high pressure during the injections, thus producing artificial spaces in the tissues. Further, Berlinger and Nonidez do not agree entirely with the findings of Evans, since they were not able to confirm the presence of histiocytes loaded with particles of ink in the nerve fiber layer of the retina, nor were they able to detect the same cells among the individual nerve fibers of the optic nerve. While it is true that there are no lymph channels or spaces communicating directly with the vitreous in the rabbit, there is no question but that there exists a definite pathway for the passage of the histiocytes after the latter have engulfed particles of ink in the vitreous.

The findings of Berlinger and Nonidez are in contrast with recent observations by Friedenwald and Chan, who found that melanin from the eyes of animals when injected into the vitreous of albinic rabbits is ultimately delivered to the retina, where it is phagocytosed by Müller's fibers. Apparently, melanin, although taken up by histiocytes, is not eliminated via the optic nerve, but remains within the eye for long periods. This may be due to the fact that melanin is not a substance foreign to the eye, as is the case with india ink.

Berlinger and Nonidez were inclined to question Evans' statement that "particulate staining is not adaptable to a study of the lymph flow in the sense of dissemination by stream flow, because the tissue cells pick up particles and apparently wander through certain retinal structures without reference to hypothetic or actual channels." They stated that Evans confused two essentially different facts, namely, (1) the passive penetration of particulate matter into preformed channels and (2) the ultimate fate of the injected material. For example, a very small amount of india ink introduced into a lymphatic channel will soon enter the sinuses of some of the nodes in the vicinity. It will remain in the sinuses if the animal is killed soon after the injection, but will be phagocytosed by histiocytes and ultimately transported into the parenchyma of the node if the animal is allowed to live. Phagocytosis of the particles in this case could not be used as an argument against the continuity of the lymphatics and the sinuses of the node, for the direct penetration of the ink into the latter is in itself convincing proof of the existence of definite channels for the flow of the lymph through the node. It seemed to them that the failure of the ink to enter the hypothetic space surrounding the central vessels in the optic nerve soon after the injection was perhaps the best proof that this space does not exist as such, its place being taken by a system of irregular interstices between the fibers of the perivascular connective tissue.

Rabbits were used for the experimental work. From 1 to 4 minims (0.06 to 0.24 cc.) of india ink was used for the injections into the vitreous. When 1 minim was used, no disturbances were observed in the eye, the ink being completely removed within five or six days. The injection of larger amounts caused marked reaction in the eye soon after the injection. The vitreous became cloudy, and there was marked iritis, with increased intra-ocular tension. Although some

rabbits were kept alive for long periods after the large injections, recovery never took place, the eyes being permanently damaged. At autopsy it was found that, in addition to a heavy infiltration of cells in the vitreous, there was in most cases detachment of the retina. The further details of the experimental work are deliberately omitted from this review.

The histopathologic work is divided into two large considerations: (1) the removal of particles after injection of 1 minim of india ink, and (2) the removal of particles after injection of a large amount of india ink, from 3 to 4 minims. In the eyes into which india ink had been injected, the perivascular connective tissue of the nerve on the side of the injection contained large numbers of cells. Some were small and rather round, and did not contain particles of ink in the cytoplasm, while others were loaded with ink.

From their observations the authors conclude that the small, round cells were young phagocytic elements on their way to the vitreous. The cells under consideration closely resembled lymphocytes. However, when they were studied under an oil immersion lens it could be seen that they did not possess typical lymphocytic nuclei, but contained a network of chromatin which was not condensed into large blocks or particles. The nuclei were often somewhat irregular in outline. Slightly larger cells with similar nuclei and more abundant cytoplasm also occurred in the vitreous. The cytoplasm was finely granular and of irregular contour. Many of these cells contained a few engulfed particles of ink. As the cells grew, their nuclei became more irregular and many showed lobulations. The cytoplasm contained more particles of ink and large vacuoles. A few cells gliding along the fine fibrillar material that separated the layers of the vitreous appeared elongated and closely resembled fibroblasts. They also contained engulfed particles of ink.

The characteristics just mentioned permitted the identification of the phagocytic cells as typical histiocytes, wandering into the vitreous. They were much more numerous in the eyes into which larger amounts of ink had been injected.

A careful study of the perivascular connective tissue of the optic nerve shortly after the injection of ink into the posterior portion of the vitreous body showed that this was the main route utilized by the young histiocytes, both on their way toward the vitreous and on their return after having engulfed particles of ink. There were, therefore, two cell streams running side by side, but flowing in opposite directions. One was represented by elements traveling toward the vitreous, about to perform their phagocytic function, while the other consisted of cells which, after having engulfed particles of ink, were transporting them through the perivascular connective tissue toward the pial sheath surrounding the nerve. Since the perivascular connective tissue is continuous in many places with trabeculae arising from the pial sheath, it was not surprising to see ink-laden cells following these trabeculae. These cells, however, were not as numerous as would be expected, and most of them soon disintegrated. In this way, ink particles were released in the pial septums. Ink-laden cells migrating among the nerve fibers were not seen. Their passage among the nerve fibers would be prevented, according to the authors, by the close meshwork of the prolongations of the glia cells.

As the cells containing ink approached the periphery of the nerve they appeared more crowded. Many cells did not continue their migration along the central vessels, but entered the pial sheath, traveling amid the connective tissue fibers of the latter for varying distances. Other ink-laden histiocytes eventually entered the dura. Such cells appeared considerably elongated as they traveled among the stout connective tissue fibers that formed this sheath. No histiocytes containing ink were seen entering the subarachnoidal and subdural spaces. Most of the cells not entering the pia and dura proceeded along the perivascular connective tissue and were apparently lost among the tissues that filled the space between the eye and the walls of the orbit.

In concluding, the authors emphasize the fact that the ink-laden histiocytes followed a definite pathway and did not enter the retina; nor did they migrate between the fibers of the optic nerve. Sections of the chiasm showed that the histiocytes bearing particles of ink never reached this region. On the other hand,

sections of the opposite eye in which no injection was made similarly indicated that no ink-laden histiocytes reached this eye or even penetrated the optic nerve.

It is of interest that, in a footnote, the authors call attention to a variance here from the recent findings of Krug, who had observed the passage of fat droplets from one eye to the other by the optic chiasm. It was clearly understood in their work that the injection of a large amount of ink into the posterior region of the vitreous called forth the usual migration of histiocytes and produced a series of disturbances through increase in intra-ocular tension, which caused permanent injury to the eye. This enormous increase in phagocytes did not visibly interfere with the removal of ink from the vitreous, although it may have retarded it considerably.

The study is of interest to the neurologist as well as to the ophthalmologist in that it dealt with the histology of phagocytes in the highly specialized nerve tissue structures in the posterior segment of the eyeball.

SPAETH, Philadelphia.

THE CRIMINO-BIOLOGICAL SERVICE IN BAVARIA. THEODOR VIERNSTEIN, J. Crim. Law & Criminol. **23**:268, 1932.

Bavaria was the first among the German federal states to introduce in the penitentiaries the system of graded punishment, or the so-called progressive system. This system, the aim of which is the correction of the offender, is necessarily based on as thorough a study of each prisoner as is possible. All convicts eligible for the system of graded punishment by reason of the length of their terms, which must exceed four months, are subjected to a medical examination. The examination is made primarily by the prison physicians. A questionnaire is used. The questionnaire asks, first, for data on the biologic heredity, both paternal and maternal, of each convict. In securing the data, information from as many members of the family as possible is secured by questioning the parents, their brothers and sisters, the brothers and sisters of the convict and also his grandparents, both paternal and maternal. Every effort is made to ascertain in regard to each of these persons not only the name, age, vocation, place of residence, year of death and ailment which caused death but the peculiarities of character, social behavior, physical or mental qualifications and defects and criminal tendencies, if any. These data are followed by accurate records of the convict's life history, his youth, the influences that dominated his bringing up, his scholastic career, his selection of a trade and changes of trade, his journeyman's years, his military service, his participation in the World War and his marriage. Finally, the exact dates and categories, as well as the internal and external causes, of all his previous criminal offenses are ascertained; such factors as dipsomania, debauchery, unemployment, distress, adversities and possible marital difficulties are searchingly investigated.

The fact that the prisoner relates these data about himself enables the examining officer to form a more or less complete picture of his character, responsiveness, intellectual qualifications and emotional make-up, and of the nature of his volitional control. A prisoner will in the majority of cases talk openly to an examining officer who treats him with the required degree of human sympathy. In cases in which the prisoner manifests intentional reserve and refusal, his very taciturnity will enable the examining officer to draw important conclusions with regard to his basic character. Accordingly, success in diagnosing character is to a certain extent assured under all circumstances, regardless of how the prisoner reacts to the necessity of making statements concerning himself, his past life, his family, his criminal tendencies and his motives.

In addition, each prisoner is examined anthropometrically and clinically.

The conclusions derived from all the items of information, and particularly from the survey of the psychologic and character make-up, yield on the one hand the social prognosis and on the other hand a knowledge of individual traits of character which may be of use for correctional treatment.

Prisoners who are not subject to examination by physicians are examined and classified by jurists, clergymen and teachers attached to the penitentiaries. Such

examinations are conducted by means of the same questionnaires, from which, however, specifically medical items pertaining to biologic heredity, psychiatry, anthropology and clinical examination are eliminated; the questionnaires used are in an abridged form, therefore, restricted to data of a sociologic and a psychologic nature.

The results of both kinds of surveys made on prisoners entering the penitentiaries are considered as provisional; they are accordingly verified or amended during the term that the convict is serving. At the expiration of the term an estimate of the social prognosis is made in the form of a final report. Copies of the reports and of all enclosures and appendixes are collected in the Bavarian Central State Crimino-Biological Bureau. The bureau also, from these data, renders expert criminobiologic opinions in recidivist cases. It cooperates with the Bavarian State Bureau of Statistics in compiling criminal statistics along biologic lines, and also keeps a card for each person mentioned in the detailed biologic reports as belonging to the family or to the environment of the convicts; each of these cards bears the full name of the person and the number of the report from which it was taken. In time a complete inventory of the criminal class will thus be compiled; at present the number of cards is about 70,000.

It is impossible to judge after the few years that the system of graded punishment has been in operation whether and to what extent the reforming of a criminal is a success. The experience gained by the personnel of the penitentiaries shows without doubt that in a large number of criminals the chances of reform are unfavorable and that no hope can be entertained for their social readjustment. First, a good many criminals are unable, because of their inner psychic make-up or because of their intellectual, psychopathic or other inferiority, to comply with the standards of society as defined by the provisions of the penal law. Second, the permanency of the unfavorable outer conditions of life to which the criminal perforce returns on completing his sentence abets relapse and breeds new crimes, even though at times the criminal may have social instincts and sufficient volitional control.

For the time being the question of a lasting social readjustment should be treated with great reserve; however, during the last ten years in Bavaria, through the system of punishment graded on a psychologic basis and through an entirely new technic of handling criminals, there have been certain satisfactory results. Disciplinary punishments for all sorts of refractoriness have shown a sharp drop; the atmosphere of the prisons has grown calmer, and hardships of confinement have been mitigated, particularly the hardships which in the days of strict incarceration tormented some of the convicts far beyond the measure of the intended punishment, brought them into a false attitude with regard to their position for which they alone were responsible, incited them to rebellion and in the long run embittered and antagonized them against human society rather than deterred them from crime.

PEARSON, Philadelphia.

ASSOCIATION OF SCLEROSIS OF THE CEREBRAL BASAL VESSELS WITH OPTIC ATROPHY AND CUPPING. ARNOLD KNAPP, Arch. Ophth. **8**:637 (Nov.) 1932.

Optic atrophy with excavation of the disk and especially with marginal cupping, as seen in glaucoma, is a puzzling condition when the intra-ocular tension is persistently low. In these cases the ophthalmologist is inclined to make a diagnosis of glaucoma, notwithstanding the subnormal tension.

It has long been known that the optic nerves may be affected in arteriosclerosis of the larger vessels at the base of the brain. As early as 1852, Türck described visual disturbances from compression of the basal optic pathways in cerebral disease, and showed that the optic nerve suffered when the arteria corporis callosi was affected, and further that the posterior communicating artery and internal carotid may compress the optic tracts. Herman Knapp, in 1875, described a nasal field defect in a case in which the internal carotid pressed on the lower and outer surfaces of the optic nerve, thus affecting the uncrossed bundle. Otto reported four cases of arteriosclerotic disease of the internal carotid and ophthalmic arteries which,

on anatomic examination, showed a dilated and hardened vascular lumen causing atrophy of the optic nerves by mechanical pressure. Liebrecht reported seven cases of arteriosclerosis of the internal carotid and ophthalmic arteries, and expressed the belief that the optic nerve suffers more frequently than is generally recognized. According to this author, pressure is not exerted in the optic canal alone but in the following three places: (1) in the fibrous optic canal by the ophthalmic artery on the optic nerve; (2) by the ascending internal carotid against the falciform dural fold; (3) midway between the canal and chiasm where the internal carotid artery and anterior cerebral artery cross under and over the optic nerve. Wilbrand and Saenger and Marburg believed that the changes in the optic nerves do not result from pressure, but are atrophic and result from nutritional disturbances, the arteriosclerosis of the smaller vessels causing perivascular softening on account of the impervious walls of these vessels.

These conditions were found at autopsy; there was no information available about the clinical ophthalmic findings. Hornicker was the first ophthalmologist to report that sclerosis of the basal cerebral vessels can be demonstrated in the living by means of the x-rays. This was in 1924. Pincherle demonstrated that in pictures of the patient in profile calcification of the internal carotid in the cavernous sinus appeared as a horizontal line or shadow in the sella, and that in the anteroposterior view it appeared as a vertically placed shadow at the inner extremity of the superior orbital fissure. Schüller, who was Pincherle's director, said: The calcification of the basal cerebral arteries appears in the roentgenogram as delicate shadow bands or as linelike double contours, rings or ring segments which in the profile view appear in the region of the sella turcica, while in the anteroposterior view they appear in the superior orbital fissure or in the optic canal. According to the degree of tortuosity and dilatation of the diseased arteries, the form and position as well as the caliber of the corresponding shadow pictures vary. Aneurysms of the basal arteries usually are recognized in the x-ray picture by calcified shells in the walls of the vessels, which project as delicate arcuate shadow lines in the region above, to one side or behind the dilated sella.

Before Knapp continues with the description of his cases of sclerosis of cerebral vessels with atrophy of the optic nerve, he reviews briefly reports of certain cases which have appeared in the literature. It is of interest that in all these there were various diagnoses. In one instance a corneal scleral trephining was done in spite of normal tension; following the operation, with reduced ocular tension, the cupping increased and the patient became blind. The author's ten cases are then reviewed.

The x-ray photographs were all taken by two men. The photographs were not easy to take, the changes often being faint and difficult to demonstrate because the bones were osteoporous and because most of the patients were old and did not remain motionless while the pictures were being taken. As at times deposits occur in the hypophysis or in the diaphragm of the sella, stereoscopic photographs, as Thiel pointed out, are essential to identify the necessarily extrasellar shadow of the internal carotid. Sosman did not think that the calcification of the arteries alone explained the changes in the optic nerves. He believes with Schüller that the changes are due to thickening of the arterial wall inside the optic canal, which may occur with or without calcification, and that when calcification is observed it simply gives one a better and a more general idea of the conditions of the patient's basal arteries.

A summary of Knapp's ten cases is given in tabular form. It is of interest that the pictures in two of the field defects were slightly suggestive of the nasal step of glaucoma. In all of the cases, the defects were quite irregular. They showed varying degrees of altitudinal hemianopia, varying degrees of binasal anopia, central field defects, unilateral defects and a combination of these with more or less marked concentric contraction.

The author's comment at the close of the paper recapitulates the findings, emphasizing the tendency toward altitudinal defects and the dissimilarity of these from glaucoma fields. He also emphasizes the calcification of the internal carotid

and of the posterior communicating and ophthalmic arteries, and the general symptoms which are those of a moderate general arteriosclerosis without particular cerebral manifestations.

SPAETH, Philadelphia.

THE STRIATAL BLOOD PICTURE OF SATO-YOSHIMATSU. C. BERLUCCHI, Riv. di pat. nerv. **40**:23 (July) 1932.

Berlucchi investigated the importance of the striatal blood picture, so denominated by Sato-Yoshimatsu, which is that under certain acute organic conditions of the central nervous system, the reaction for oxidase in the blood appears normal while that for peroxidase appears negative. In eliciting the reaction for peroxidase a smear of blood is allowed to dry on a slide; a 50 per cent solution of copper sulphate is then poured on the slide, followed by a watery solution of benzidine (20 cg. of benzidine, in 200 cc. of water — to the filtrate of which 4 drops of a 3 per cent solution of hydrogen dioxide are added). Following the action of the benzidine, the peroxidase appears stained intensely blue. A counterstain may be added in the form of saffranine, neutral red or fuchsin. The smear is mounted in a dilute solution of the same dye that is used for counterstaining.

In control material, Sato and Yoshimatsu have never found a disappearance of the peroxidase reaction in conditions other than acute epidemic encephalitis; they think that the disappearance of peroxidase in the white cells of the blood must be specifically related to epidemic encephalitis. They also think that this disappearance is due not to a direct action of the virus on the blood, but to its action on the central nervous system and, precisely, on the corpus striatum. Hence the term striatal blood picture is derived.

Experimentally, Sato has worked with rabbits in the blood of which the staining reactions of oxidase and peroxidase do not differ from those in human blood. The cat's eosinophilic cells, however, contain no oxidase or peroxidase. The guinea-pig's basophilic leukocytes contain oxidase but not peroxidase. Some invertebrates normally reveal an absence of peroxidase.

In his experiments in rabbits, in which he produced injuries on both sides of the corpus striatum, Sato succeeded in effecting a disappearance of the peroxidases while the oxidases were still present. The operation was called by Sato the peroxidase puncture. To bring about the disappearance of the peroxidase the lesion had to be of such an extent as to determine the death of the animal in a short time. Later, Sato expressed the opinion that the centers responsible for the presence of peroxidase in the blood are located in the mesencephalon. Shoji, experimenting on the mesencephalon of rabbits, was able to reproduce the striatal blood picture in only 7 of 227 animals operated on. Peroxidase is poured into the circulating blood by the glands of internal secretion. When the production of the peroxidase is involved, the replenishment of the white cells with this substance gradually ceases, and the striatal blood picture is gradually established.

Sato and Yoshimatsu's investigation may have an important application in establishing the repercussion of involvement of the central nervous system on the biochemical constitution of the blood. Little work has been done in clinical neurology in relation to this particular investigation. Only here and there in the literature are there reports of cases investigated in connection with the striatal blood picture. One of the few cases was reported by Lehenkuhl in 1927; it was that of a boy, aged 3, who had sudden fits of spasm in the flexor muscles of the thighs and in the sternocleidomastoids. A case of recurrent chorea was described by Simmel in 1931, in which there was the same blood picture. The third case was described by Haenkel; it was that of a woman, aged 49, suffering from pneumonia accompanied by motor hyperactivity referable to chorea. In these three cases, the clinical diagnosis of a lesion of the corpus striatum was established. Contrasting with such positive results, Sartorius, in a group of cases, most of which were involvements of the extrapyramidal system, reported normal reactions for both oxidase and peroxidase.

Berlucchi has studied 50 cases of lesions of the central nervous system, and has always found normal reactions for oxidase and peroxidase. According to him, it follows that judgment must still be held in abeyance concerning the value of the Sato-Yoshimatsu striatal picture of the blood. He believes that the statement that in the corpus striatum a center exists which might control the output of peroxidase is somewhat daring. If one takes into consideration the fact that, in the experimental work, following the surgical procedure there is a general severe reaction leading to death, it seems difficult to establish a localized center for the changes in the blood. It also follows that investigation of the striatal blood picture should not be limited to subjects with involvement of the nervous system, but should include subjects suffering from general medical conditions with disturbance in the blood chemistry, even if apparently independent of the nervous system. In conclusion, the author reserves a final opinion until more convincing clinical and experimental material is available. FERRARO, New York, N. Y.

MYASTHENIA GRAVIS: NEW DIAGNOSTIC EYE FINDINGS, WITH POSSIBLE PATHOLOGIC SIGNIFICANCE. S. V. ABRAHAM, Arch. Ophth. **7**:700 (May) 1932.

Myasthenia gravis was first described by Wilkes in 1877. Much important literature has appeared since that time. The present article briefly defines the condition as a symptom complex characterized by sudden, intermittent and progressive clinical weakness of a muscle or muscle group, often terminating in death and leaving almost no pathologic changes despite the marked changes during life.

Some of the various ocular conditions found are outlined. According to Starr, ptosis or diplopia is a first symptom in 40 per cent of cases. Bielschowsky states that ptosis is present in 80 per cent of cases. While not perhaps the first symptoms in matter of time, the ocular symptoms are often the first for which a physician is consulted. The ptosis may be in one or both lids, and is usually most marked in the morning after rest. Sometimes the ptosis is more marked on one side than on the other. Exercise or emotional upsets also increase the severity of the symptoms. Limitation of ocular movements is frequent and subject to daily variation. The pupillary reflexes are usually normal, and in emotional patients they seem to be sluggish. There were no sluggish reflexes reported except in cases of extreme prostration. Posey did not believe that the nystagmus reported was true nystagmus. Lid-lag has also been reported. In addition to these, some other symptoms of interest to ophthalmologists are outlined, especially the electrical test in muscle degeneration. The author states that the changes which occur do not clearly assume a muscle weakness. He draws a similar picture of the ocular changes, which also are not consistent with the idea of muscle weakness.

Abraham, in working on these cases, utilized his method of measuring heterophoria, which is based on an insurmountable amount of diplopia in one direction or meridian while measuring any manifest deviation in any other direction or meridian. The condition that permits this is the almost complete suspension of fusional effort. The eyes at this time apparently take a position of relative rest, permitting the measurement of maximum heterophoria. On the basis of this work, he points out that if vertical prisms are used to produce the diplopia, the images are then separated in space by an amount directly proportional to the amount of prism used, even though the patient has only a moment before been able to overcome almost the entire amount of prism now before the eye. Apparently, then, the ocular muscles immediately relax almost completely on suspension of fusion, a condition that does not exist in the myasthenic patient.

The author presents a series of eight cases to prove his point that testing for heterophoria is a new diagnostic method for myasthenia gravis. About 1,000 such tests were made. The cases included at least six of epilepsy, seventeen of chorea, six of paralysis agitans, six of chronic encephalitis, one of encephalitis,

nineteen of multiple sclerosis, three of progressive muscular atrophy, one of progressive muscular dystrophy with an unusual sensory involvement, one of pernicious anemia with cord changes and about twenty of syphilis of the central nervous system.

Only in myasthenia were the results markedly variable as to the demonstrable heterophoria or the ductions. "Although in the light of Sherrington's principle of reciprocal innervation, relaxation of antagonists is an important element in the contraction of a muscle, the major work in maintaining fusion, for example, is done by the contracting muscles. This and the modus operandi of prisms force the interpretation of the data given as indicative of abnormally strong muscles with astonishingly increased and continued activity."

As a result of the experimental work, the author properly formed the following conclusions: "The irregularity in the amount and quality of the heterophoria in the short span of a few moments, the irregularity in duction readings, the unusually high duction reading, the close proximity of the images when diplopia is produced, the approximation of the amount of prism used in creating the diplopia and the hyperphoria as measured by the Maddox rod test and the actual turning of the eye in the direction of the apex of the prism—indicating that the muscle stimulated does not 'tire'—permit of but one interpretation, namely, that the muscle or muscles stimulated contracted, but failed to relax promptly or completely, remaining in a prolonged contraction state. Such findings obtain in no other condition in which tests have been performed, and therefore would seem of diagnostic value in this condition."

The third conclusion is stated without any qualifying note by the author, and is quoted verbatim: "From these findings I am led to conclude that myasthenia gravis is not a true myasthenia."

SPAETH, Philadelphia.

OBSERVATIONS ON THE ALTERATION OF THE CIRCULATION OF THE BRAIN BY SURGICAL MEANS IN DISEASES OF THE CENTRAL NERVOUS SYSTEM. N. D. ROYLE, Brit. M. J. **1**:1063 (June 11) 1932.

The operation of section of the sympathetic thoracic trunk profoundly alters the cerebral circulation. This is borne out by the findings reported by Royle. Stimulation of the cervical sympathetic trunk in the region of the stellate ganglion demonstrated a constriction of the vessels of the brain and a visible shrinking away from the parietes. Division of the thoracocervical sympathetic trunk on the left side at its exit from the thorax, in a goat, led to a rise in temperature on the left side of the face and ear, partial collapse of the left nostril and movement of the whole lower jaw to the right; the left eyelid drooped. There were both ipsilateral and contralateral effects. There were also neurologic changes. At a certain stage of anesthesia the limbs of the goat became rigid as in decerebrate rigidity. This was altered by cutting the cervical sympathetic trunk. With the animal on its back after section of the trunk the contralateral limbs exhibited a loss of tone. Extension did not appear in them, and there was a complete loss of resistance to passive movements. There were other definite neurologic differences between the two sides. When the skull was opened, the blood vessels were observed to be smaller, and anastomoses were less frequently seen on the ipsilateral than on the contralateral side. The whole of the contralateral side was congested and blue. This observation was confirmed in a second goat. After decerebration, with the animal on its back, extension appeared in the ipsilateral limbs, but the contralateral limbs remained flexed. The contralateral limbs took up the position determined by gravity, while the limbs on the ipsilateral side remained extended. Lumbar sympathectomy had been performed on this animal six months previously. This was on the same side as the section of the thoracic trunk. Extension appeared in the ipsilateral hind limb in spite of the ramisection which had been previously performed. The reflexes in the neck were also affected.

Following section of the thoracic sympathetic trunk in human beings, the immediate changes on the same side as the section are as follows: (1) diminution

of tone of muscles of the face and of the upper limb; (2) sluggishness in the fall of the eyelid; (3) contraction of the pupil; (4) cessation of sweating at that side of the face and forehead and on the upper limb; (5) circulatory changes; (6) an increase in temperature; (7) drooping of the eyelid.

The chief change on the contralateral side following section of the thoracic sympathetic trunk is an alteration in tonus in the muscles of the whole side, but this is not so noticeable in the face. It is greater while the patient is under anesthesia. There are also a change in the clonus exhibited by spastic limbs, a greater range of passive movement and a diminution of rigidity. In parkinsonism with tremor, there is an immediate diminution of tremor which ceases altogether in a few days. The author believes that the tremor of parkinsonism may be cortical in origin. He thinks that tonus is bound up in some way with the function of the sympathetic nervous system, and that it represents a reflex function of the spinal centers.

A patient who had previously been cranky and bad tempered and who had suffered from spastic hemiplegia responded with satisfactory mental changes after section of the sympathetic cervical trunk Congenital spastic hemiplegia was markedly reduced after section of the sympathetic thoracic trunk. In four patients suffering from trigeminal neuralgia, complete relief was obtained after section. Relief is obtained in retinitis pigmentosa if the patient retains central vision. Raynaud's disease is also corrected. Subjective and objective symptoms following encephalitis were improved. Physical symptoms associated with a congenital mental defect were markedly improved following operation. Congenital deafness was also markedly relieved. In another patient the headache of retinitis pigmentosa was relieved. This method did not prove to be a successful form of treatment for epilepsy in adults, though it did offer encouraging results in children.

FERGUSON, Niagara Falls, N. Y.

CLINICAL OBSERVATIONS ON TABETIC ARTHROPATHIES (CHARCOT JOINT). J. ALBERT KEY, Am. J. Syph. **16**:429 (Oct.) 1932.

Charcot's joint is a rare condition. Only from 4 to 10 per cent of tabetic persons present this complication. It usually occurs in the fifth or sixth decade of life. In a study of sixty-nine cases, Key found that the average duration of the syphilis before the appearance of the arthropathy was nineteen years. Typically, the disease begins as a sudden spontaneous swelling of the joint, which may become marked within a few hours. Injury or pain seldom precedes the swelling. The lower extremity is affected in the vast majority of cases, the author having found only four instances of involvement of the shoulder, elbow or wrist in almost one hundred cases of Charcot's joint. As the swelling increases, dull aching pain is experienced by the patient, but the severe nocturnal exacerbations characteristic of osseous syphilis do not occur. After one or more months, the acute symptoms subside, and the arthropathy enters the chronic phase, with progressive disintegration of the joint. Physical examination of the area reveals local swelling, with obliteration of the contour of the joint, the skin being tense and shiny but not reddened. The swelling is firm and does not pit on pressure. Although there is no muscle spasm, motion tends to be limited because of the swelling and excess fluid. In the chronic phase, the capsules and ligaments stretch so that abnormal mobility develops.

In about a third of the patients in Key's series, the arthropathy was the first subjective evidence of disease. Sooner or later, however, they all presented fairly typical pictures of tabes dorsalis. The roentgen rays afforded a valuable diagnostic aid, revealing swelling and increased density of the soft tissue, changes in the structure of the bones, erosion of the bearing surfaces, production of new bone, pathologic fractures, loose bodies in the joints, calcification in the periarticular surfaces and various subluxations and dislocations. Perhaps the most distinguishing feature of the Charcot joint is the pathologic fracture. This is the result of mechanical stress, and involves the articular surface. The fracture may

occur without the knowledge of the patient, and there is seldom a history of antecedent trauma. The foot is the favorite site for pathologic fracture. The author analyzes in detail the diagnostic differentiation between Charcot joint and various other arthropathies and arthritides, a tabulation which should be read in full in the original paper. The forms of arthritis especially differentiated from tabetic arthropathy are the tuberculous, gonorrheal, hypertrophic, infectious and traumatic types.

Antisyphilitic treatment in the early stages of locomotor ataxia probably cannot prevent the appearance of Charcot's joint. It seems to the author ineffective. Active therapy may be conservative or operative, the former consisting of rest, physical therapy and properly graded exercises. Rest should be assured by immobilization. Heat is the most effective physiotherapeutic agency, and should be given in the form of infra-red rays, diathermy or hot fomentations. Patients under 60, in fairly good physical condition, should be offered the benefit of surgical intervention. For spinal arthropathy, stabilization with a tibial graft is recommended; a Charcot hip may be treated with a reconstructive operation or by means of extra-articular and intra-articular arthrodesis. At the knee, arthrodesis is often highly successful; amputation is resorted to in instances of marked disintegration. The ankle joint seldom needs surgical care, although an osteotomy may be undertaken to correct a valgus or a varus deformity. Pathologic fractures respond almost as well as ordinary fractures to intensive intelligent treatment.

DAVIDSON, Newark, N. J.

THE RELATIONSHIP BETWEEN THE STRIATUM AND THE LIVER. HANSI LOEVY, Nervenarzt **4**:653, 1931.

Since ancient times the relationship between the brain and the liver has aroused the interest of clinicians. Yellow discoloration of basal ganglia and other gray nuclei of the brain stem in severe jaundice of the new-born (kernicterus neonatorum), the association of lenticular softening with cirrhosis of the liver in Wilson's disease and related syndromes, the occasional postmortem finding of parenchymatous alteration of the liver in cases of senile paralysis agitans and in cases of chronic postencephalitic parkinsonism have been much discussed in the literature of the last three decades. Kernicterus, paralysis agitans and parkinsonism are not appropriate conditions for the study of the relationship between lesions of the striatum and those of the liver. The etiology of kernicterus of the new-born is unknown. The yellow pigmentation of the basal ganglia in this disease points merely to a particular affinity of this region of the brain for the biliary pigments (as for carbon monoxide and manganese). Paralysis agitans is a general involutive process and the liver as well as the brain may therefore be affected by the same vascular (arteriosclerotic) changes. In postencephalitic parkinsonism there is a general infection; therefore the liver and brain may again be affected coincidentally and yet independently of each other.

The nosologic group of hepatolenticular degenerations (Wilson's disease and pseudosclerosis) are more appropriate for the study of the problem. The patients are young, and the factor of infection is generally in abeyance. Hence, the author reviews a series of recently published cases of this nosologic group and studies the time relationship between the onset of striatal and of hepatic symptoms. There are as many cases in which the disease of the liver appeared first as cases in which the striatal disease appeared first. Loevy studied also the incidence in these cases of the following four typical components of the hepatolenticular syndrome: (1) the spongy degeneration of the basal ganglia peculiar to the wilsonian type of the syndrome; (2) the glial proliferation with presence of the so-called "Alzheimer's cells" characteristic of pseudosclerosis; (3) the Kayser-Fleischer corneal ring, and (4) hobnail cirrhosis of the liver. He found that these four components of the syndrome occur in most varied combinations without any constant relationship to one another.

On the grounds of this study, Loevy believes that in the group of hepatolenticular degenerations the lesions of the liver and brain do not stand in any causal relationshp to each other but develop as coordinated parallel processes. The prevalently familial occurrence of these regularly coinciding lesions and their recessive character are particularly important. The essential points are that the four cardinal components of the pathologic picture of this nosologic group may be met with in different cases in any number of combinations, that these diseases occur with particular frequency in families with hereditary neuropathic predisposition, and that they may alternate with other diseases of the liver and nervous system. It may be assumed, therefore, that there are combined hereditary factors which create an increased vulnerability of the liver and the brain.

YAKOVLEV, Palmer, Mass.

ENCEPHALOPATHY DUE TO CHRONIC PLUMBISM. THEODORE S. EVANS, Arch. Int. Med. **49**:735 (May) 1932.

A case of lead poisoning in which good results were obtained with the treatment by mobilization, and in which de-leading precipitated tetanic convulsions, is reported by Evans. A plumber, aged 45, who had handled red lead all his life, suffered with an attack of diarrhea and abdominal cramps in 1925; in 1926 he complained of mental confusion, incoordination, pain in the back, weakness of the legs and twitchings of the arms. When examined in April, 1927, he displayed pallor, a lead line on the gums, exaggerated equal reflexes and lead in both urine and feces. The blood pressure was 120 systolic and 80 diastolic, and never exceeded 130 systolic at any time during the illness. The hemoglobin in April, 1927, was 85 per cent, and there were no stipple cells.

Treatment during the first four days consisted of the administration of 4 cc. (1 drachm) of syrup of hydriodic acid every three hours; during this phase of the treatment the output of lead in the excreta increased. Mobilization was attempted on the fifth day, calcium lactate 1 Gm. and 1 quart of milk (1,000 cc.) (each twice a day) being given. In a month the lead line had disappeared, and clinical improvement was marked. Lead disappeared from the urine and feces. In January, 1928, the patient was sufficiently improved to permit de-leading. This was done by giving 1 Gm. of ammonium chloride every hour and by requiring the patient to adhere to a calcium-poor diet. Included in the dietary were meat, liver, potato, rice, fruit and all milk-free foods; forbidden were milk, eggs and green vegetables. Early in March, the patient reported that he had never felt better in his life; but on March 11, 1928, he experienced a series of tetany-like convulsions, with periods of pronounced cyanosis and marked apnea; each seizure began with twitching of the muscles of the right eye and spread to the entire body. Chvostek's and Trousseau's signs were elicited between attacks. Following the intravenous administration of 60 Gm. of calcium chloride, the patient experienced relief. During the next six months he was well, but in the fall of 1928 he began to become worse. Headaches, confusion and right hemianopia appeared. In December, 1928, a second series of convulsions occurred; they were similar in type and in response to treatment to the earlier seizures. The patient gained very slowly, his mental state remaining confused, and he died in November, 1929, of acute bronchopneumonia.

The case is almost certainly one of lead encephalopathy; the chemical components of the blood and urine rule out uremia, while the result of treatment makes the diagnosis of multiple sclerosis unlikely. That the convulsions were in the nature of tetany seems to be borne out by their appearance while the patient was on a low calcium diet, by spectacular improvement following treatment with calcium and by the existence of the Chvostek and Trousseau phenomena. The second spell occurred in the course of a diarrheal disease when the gastro-intestinal tract was unable to absorb ingested calcium.

DAVIDSON, Newark, N. J.

FUNDAMENTAL PRINCIPLES AND TECHNIC OF SURGICAL TREATMENT OF TUMORS OF THE CEREBELLUM. J. ESTELLA, Arch. Fac. de med., Zaragoza **1**:1 (Jan.-Feb.) 1932.

Estella states that in the surgical treatment of tumors of the cerebellum the operation in two stages seems, at the present time, to be the most generally accepted type of intervention, especially so in cases in which the tumor is located in the posterior fossa and in which the approach demands the performance of complicated maneuvers that may give origin to intense shock and to abundant hemorrhage. However, the aggravation that follows the palliative trephination in cases of tumors of the posterior fossa is one of the best arguments one can offer against the operations in two stages. It has been found also that sudden death following craniectomies (performed in cases of intracerebellar tumors as a preliminary operation) without the resection of the tumor was caused by the direct compression of the bulb by the tumor, which might have been avoided by a primary radical operation with resection of the tumor. The author reports a case in which necropsy confirmed his statement, and, basing his belief on his experience and after a wide review of the literature, he concludes that: The operations in two or more steps for the resection of tumors located in the posterior fossa are associated with a higher operative mortality than the operation in only one step, that is, the resection of the tumor in a primary radical operation. A great number of deaths among patients in whom the latter type of operation is used occurs in the interval between the first (preliminary) and the second (resective) operations. They are caused either by the gravitation of the tumor on the bulb or by the obstacle that the presence of the tumor offers to the circulation of the cerebrospinal fluid. In the first case, the patients show a clinical syndrome of direct compression of the bulb, with rapid evolution and sudden death. Necropsy proves the mechanical action of the tumor on the bulb and on the bulbar protuberance. In the second case, the patients die of ventricular hyperpressure. In other cases, the cause of death is another of the well known dangers that are inherent to the resection of the tumor in a secondary operation. The primary radical operation constitutes the best preventive means against the failures following the preliminary operation for the surgical treatment of intracerebellar tumors; it seems advisable to accept it as the operation of choice, when there are circumstantial contraindications. Certain details of technic, such as a sitting position during the operation, the use of local anesthesia, the performance of a wide trephination with an autoplastic flap (according to De Martel's technic as shown in the illustrations), the use of continued aspiration of the hemorrhagic fluids during the operation and of the electric bistoury and the utilization of heterologous muscle as a biologic agent to produce direct hemostasis, are of paramount importance in relation to the good results to be expected. In cases of encapsulated solid tumors, the only necessary operation is the enucleation of the tumor. In cases of cystic tumors it seems advisable to perform the radical operation with wide resection of the cyst and cystic walls in order to prevent a possible recurrence.

EDITOR'S ABSTRACT.

EFFECT ON THE SKIN OF NERVOUS AND EMOTIONAL STATES: IV. THE ROSACEA COMPLEX; A REAPPRAISAL WITH SPECIAL REFERENCE TO THE CONSTITUTIONAL BACKGROUND AND THE RATIONALE OF TREATMENT. JOHN H. STOKES and HERMAN BEERMAN, Arch. Dermat. & Syph. **26**:478 (Sept.) 1932.

Eighty-six patients with the rosacea complex were studied; the histories tended to discredit the concept of a hereditary predisposition, although it is the authors' opinion that the anacidity, acne, allergic state and emotional instability often seen in these cases may represent hereditary influences. Women outnumbered men three to one, a factor due not so much to the tendency of women to seek cosmetic advice as to the exposure of women to caffeine and sugar (because of the activities of social life) and to the wear and tear on the nervous system resulting from the upbringing and disciplining of children. The average age of the patients was 32.

No special vocational or recreational habits were found. Conjunctivitis was observed in six instances. More than 80 per cent of the patients displayed the seborrheic habitus; the authors postulated that this was a manifestation of a tendency to overstore the skin with carbohydrates, thus laying the former open to seborrhea and pyogenic infections. This factor was recognized by the patients, who usually voluntarily reduced their carbohydrate intake. The neurogenic background was that of chronic wear and tear, habitual worry, overwork, insomnia, irregular hours and the gnawing of personal and family troubles. More than half of the patients in the series drank two or more cups of coffee daily. The action of caffeine seems to be due to its vasodilator effect; coffee itself acts as a gastric irritant, while the sugar ingested with the beverage further complicates the problem of evaluating the effects of excessive coffee intake. Fifty-two per cent of the patients had definite foci of infection, and in several instances removal of these foci resulted in clinical improvement. The importance of menstrual disturbances, the intake of alcohol and condiments and the allergic background seemed doubtful. Stokes and Beerman are inclined to the hypothesis that the gastric hypo-acidity characteristic of rosacea encourages the breeding of Bacillus welchii which, in turn, results in excessive production of histamine. The similarity between the effects of the injection of histamine and the dilatation of superficial blood vessels seen in rosacea is emphasized. Constipation naturally results from this gastro-intestinal condition, producing a chronic irritability of nerve tissue. The latter factor has suggested the use of calcium in the treatment of seborrheic disorders. The therapeutic program suggested includes: (1) psychotherapy to promote neuromuscular relaxation; (2) a dilute or a 10 per cent solution of hydrochloric acid, 4 cc. in lemon juice, with each meal; (3) a reduction in the carbohydrate, and an increase in the protein intake; (4) removal of foci of infection; (5) treatment with calcium, preferably with a noneffervescent form; (6) local application of x-rays; (7) topical applications of a white lotion or mild sulphur resorcinol paste; (8) elimination from the diet of coffee, tea, alcohol and hot or spiced foods; (9) instruction in reducing the speed of eating; (10) attention to allergic susceptibilities, including local contacts.

DAVIDSON, Newark, N. J.

HOW TO TREAT HEAD INJURIES AND APPRAISE THEM. F. KENNEDY and S. B. WORTIS, J. A. M. A. **98**:1352 (April 16) 1932.

One thousand cases of acute injury to the head are reviewed, each presenting one or more of the following absolute signs: (1) postmortem evidence of skull fracture or brain laceration, (2) positive roentgen evidence of skull fracture and (3) bloody spinal fluid obtained by lumbar puncture. The treatment administered was found to be highly varied. Since in 53.2 per cent of the fatal cases death occurred within the first twenty-four hours in the hospital, the authors have thought it wise to impose the following standardized therapy: 1. Shock should be treated with intravenous injections of hypertonic dextrose solution, from 100 to 500 cc. of 50 per cent sterile dextrose. 2. Lumbar puncture should be done for both diagnosis and treatment. 3. Hypertonic dextrose solution should be administered repeatedly by vein for dehydration of the brain, 100 cc. of 50 per cent sterile dextrose three times a day. 4. Caffeine sodiobenzoate should be given by hypodermic injections, 7½ grains (0.5 Gm.) every four hours. 5. By means of rectal taps or by rectal drip, from 90 to 120 cc. of 25 per cent dextrose solution should be given every four hours. 6. The head of the bed should be elevated from 15 to 45 degrees. 7. In suitable cases, antimeningococcal serum should be given. 8. Operative procedures are necessary in compound fractures requiring débridement and in cases in which middle meningeal hemorrhage is suspected. 9 Uncomplicated depressed vault fractures may be elevated after the passage of acute shock. Surgery in all such patients may often be safely postponed for several days. 10. Right subtemporal decompression should be resorted to only in comatose patients with papilledema who do not respond after three hours to this medical

regimen. To determine the degree of disability dependent on structural neural injury, the following plan is offered: A. Absolute criteria: (1) roentgen evidence of skull fracture; (2) bloody spinal fluid; (3) bleeding or cerebrospinal fluid leakage from orifices, especially from the ears, and (4) focal cerebral palsies. B. Presumptive criteria, in the order of their importance: (5) convulsive states, *proved* posttraumatic; (6) ventricular distortion, *proved* posttraumatic; (7) history of prolonged unconsciousness, and (8) history of adequate trauma. All these units are really measurable and are instrumental in establishing the fact of brain injury. The absolute criteria plus seven and eight of the presumptive criteria can be accurately determined. Headache and dizziness, on the other hand, are unmeasurable factors following injury to the head, and if they persist for more than four months in a man under 60 ununited to any of the first seven premises of brain or meningeal injury, we should believe that they arise not from structural neural change but from the adoption of an idea in agreement with an already established emotional trend; of such origin are the suggestion neuroses.

EDITOR'S ABSTRACT.

TREATMENT OF CHRONIC SUPPURATIVE DISEASE OF THE MIDDLE EAR. J. D. McLAGGAN, Brit. M. J. **2**:94 (July 16) 1932.

Chronic otitis may follow a recurrent infection of the nasopharynx. It may be associated with a chronic infection of the mastoid antrum and air cells. In some cases the bulk of the disease lies chiefly in the region of the attic. In a fourth group the tympanum bears the brunt of the trouble. Fifth, there may be gross involvement of the entire cleft of the middle ear.

In the first group the usual history is one of recurrent discharge in childhood. This usually starts with a cold or sore throat. Pain in the ear quickly follows, which may be relieved during the first attack by rupture of the drum. In subsequent attacks the drum ruptures easily, hence there is less pain. Treatment consists essentially in clearing up the infection in the nasopharynx, in addition to local treatment. The discharge in these conditions is mucous or mucopurulent. In disease associated with the mastoid antrum, tenderness is elicited over the mastoid. The discharge is purulent. In addition to local care the important treatment is drainage of the antrum and of its air cells. Chronic otitis confined principally to the region of the attic is much rarer. It is more chronic. There is a history of aural discharge for years, without cessation and without much pain; the discharge is thin and watery. The attic must be laid open by an approach through the antrum. This operation is rather delicate. Hearing is preserved. In the fourth type, in which the disease is limited to the middle ear or to the tympanum, the otitis usually follows a recurrent infection of the eustachian tube, the source of which has been cleared up. Treatment by drops and by keeping the ear clean usually leads to a cure, but when this is not carried out ionization is successful. The middle ear and the external meatus are filled with a zinc sulphate solution after the ear has been thoroughly cleansed. Into this pool is inserted a metal electrode encased in vulcanite, which is attached to the positive pole. The negative pole is attached to a flat electrode placed on the patient's arm. A current of from 2 to 3 milliamperes is passed for from ten to fifteen minutes. This may require several repetitions. In massive infection of the middle ear there is usually a history of a profuse, purulent, frequently blood-stained and usually foul-smelling discharge. Acute attacks, with pain, headache and elevation of temperature are common. There is tenderness over the mastoid. It is this type of infection which most frequently extends to the inner ear and the intracranial structures. Examination reveals gross destruction. A radical mastoid operation, removal of the diseased structures in the middle ear, effects a cure, with loss of or impaired hearing in 70 per cent of the cases.

In all these conditions prophylaxis, general hygienic measures and care are important.

FERGUSON, Niagara Falls, N. Y.

LOCALIZED MASTICATOSUDORAL REFLEX. ROBERT RENDU, Rev. d'oto-neuro-opht. **10**:465 (July-Aug.) 1932.

Rendu reports 24 cases of the masticatosudoral reflex occurring as a result of war wounds. Most of the patients had more or less serious wounds in the superior parotid region at the point of emergence of the auriculotemporal nerve, the ascending ramus of the inferior maxilla, the external auditory meatus and the mastoid process. The problem of pathogenesis is difficult, because in a few patients the trauma did not involve the parotid or the auriculotemporal nerve. It is true also that the reflex has been observed in cases of wounds in the angulomaxillary region, where the auriculotemporal nerve could not be involved. Several patients have been examined sixteen or seventeen years after the receipt of the wounds, and in only one has the reflex disappeared.

The reflex is constant, occurring in winter as well as in summer, at each repast and only with chewing. Bearing in mind Claude Bernard's dictum that the parotid secretion is a saliva of mastication, the author noted that the sweating was more abundant when the food was hard, the repast long and the mastication rapid, and when the chewing was done on the affected side. The zone of sweating was limited to the inferior part of the temporal region in one fourth of the cases; in more than half of the cases it was 1 or 2 cm. lower; in two cases there was, in addition, a zone of sweating behind the ear; in one case this zone extended to the inferior two thirds of the masseter region and in one case it extended to the nose. The sweating did not replace the normal flow of parotid saliva. One patient was annoyed by an excess of nasal secretion while eating. Disturbances of cutaneous sensibility were noted in almost all cases, being usually hypesthesia or paresthesia. The areas of disturbed sensibility were greater than the zone of sweating; they did not coincide with a determined nerve distribution or correspond always to the distribution of the nerves which could have been involved in the trauma. The zones of anesthesia or hypesthesia were not always identical with those of sweating.

The several theories hitherto advanced to explain the pathogenic mechanism in these cases are discussed; none of them have been found satisfactory. Rendu believes that the theory of diffusion of the nerve impulse is the most acceptable one. In consequence of a nerve lesion that disturbs the function of the parotid gland, the nerve impulse to the masticator fibers is diffused to the sudorific fibers, thus causing association of masticating movements with local sweating. This diffusion may even involve the gasserian ganglion. The manner of the diffusion may be compared to the trembling of a house caused by a passing truck. The whole subject remains obscure.

DENNIS, Colorado Springs.

CERTAIN PATHOLOGICAL ASPECTS OF NEUROSYPHILIS. RUBY O. STERN, Brain **55**:145 (June) 1932.

From material consisting of twenty-eight cases of dementia paralytica and the tabetic form of dementia paralytica and eight of tabes dorsalis, six cases ranging from an early mild type of dementia paralytica without treatment to a stage from ten to twenty months after malarial treatment are described. The outstanding histologic features in an untreated patient with dementia paralytica are the degenerative and proliferative changes of the ectodermal tissues; the mesodermal reactions are those of the wandering cells, of the vessels and of Hortega's "third element." The storage of an iron-containing pigment, in the absence of hemorrhage and of trypanosomiasis, is specific for dementia paralytica. Jakob found that the iron content of the rod cells was parallel with the amount of perivascular infiltration. Various views of different authors are discussed as to the histopathology of the brain after malarial treatment. The author agrees with Ferraro that there is no constant increase in the amount of perivascular infiltration during the first month after malarial treatment, and that destruction of spirochetes marks the starting point for the recession of the inflammatory exudate. The microglial reaction appeared to bear no relation to the length of time the patient survived

treatment. Jakob correlated tremors with pathologic involvement of basal ganglia. The author found lesions in the basal ganglia in sixteen of twenty-two cases in which they were examined.

Since the discovery of Spirochaeta pallida in the cerebral cortex by Noguchi in 1913, numerous workers have found the spirochetes in all parts of the brain. Spirochetes are most likely to be found in cases that presented the features of euphoria and grandiose delusions during life. Usually the spirochetes are not found in the brain following malarial therapy. The author found spirochetes in at least 50 per cent of patients not treated by malaria, whereas six months after malarial treatment it was difficult to find them. In the extracerebral pathology of neurosyphilis the clinical evidence of the association of the aorta and nervous syphilis is much less frequent than is the pathologic evidence. In dementia paralytica and tabes, syphilitic lesions of organs other than the aorta are rare. It is suggested that the toxins of the spirochetes are responsible for the lesions both in the aorta and in the nervous system. The discoveries in regard to neurosyphilis have changed its clinical course, as shown by the infrequency of tertiary manifestations in the nervous system. If the secondary phenomena are aborted by early active treatment, no immunity is produced, and the parenchymatous form of neurosyphilis results. With malaria, first the spirochetes are killed, and then a remission occurs in which immunity develops in the patient. MICHAELS, Boston.

FURTHER NOTES ON PITUITARY BASOPHILISM. HARVEY CUSHING, J. A. M. A. **99**:281 (July 23) 1932.

In a recent paper Harvey Cushing reported twelve examples of a peculiar and clinically unmistakable polyglandular syndrome. The disorder is characterized by a rapidly acquired plethoric adiposity affecting the face, neck and trunk, the extremities being spared. It is associated in women with hypertrichosis and amenorrhea. Other characteristic features are vascular hypertension, purplish striae distensae of the abdomen, and acrocyanosis with cutis marmorata of the extremities. It is often accompanied by hyperglycemia, occasionally by polycythemia, and a peculiar softening of the bones of the skeleton has been commonly found at autopsy. In its extreme forms, the malady has more often been encountered in young adults, and the average duration of life in the fatal cases has been something over five years. It is not an uncommon syndrome. Numerous typical examples have been reported, the disease in most instances having been ascribed to a primary suprarenal disorder for the reason that cortical hyperplasia is a not uncommon postmortem observation. However, in five of the eight cases that had come to autopsy an unsuspected pituitary adenoma was found, and the fact that three of them were unmistakably composed of basophilic elements made it probable, in view of the supposed rarity of adenomas of this type, that the pituitary lesion was the primary cause of the syndrome. This at least was the interpretation put on the matter, the symptomatic evidences of disordered function of suprarenal cortex, of pancreatic islets, of parathyroid glandules and of reproductive glands being looked on as wholly secondary expressions of the general endocrine derangement. Since the publication of the preceding paper, new facts have come to hand which seem further to strengthen the views therein expressed. Additional cases serve to increase the percentage of proved basophil adenomas in association with the polyglandular syndrome under discussion. Instead of only three of eight cases that had been examined post mortem, there are now six of eleven in which a pituitary basophil adenoma has been disclosed. The pituitary body in two other cases was said to be normal, but in the absence of serial sections this mere statement is no longer convincing. When one takes into consideration not only the presumed infrequency of adenomas of this type but their small size, whereby they easily escape detection, and couples this with the fact that chief attention has been paid to the condition of the suprarenal glands in all the autopsies heretofore conducted, the fact that a basophil adenoma has been found in half of the patients who have succumbed to this peculiarly unmistakable malady must be something more than coincidence. EDITOR'S ABSTRACT.

TACCONE'S REACTION IN THE CEREBROSPINAL FLUID. A. PACIFICO, Riv. di pat. nerv. **40**:1 (July-Aug.) 1932.

The author has investigated Taccone's reaction in the cerebrospinal fluid by comparing the reaction in various nonneurologic and various neuropsychiatric conditions. The reaction is produced by adding to a 5 per cent solution of potassium bichromate, to which trichloracetic acid has been added, 0.5 cc. of cerebrospinal fluid, which is layered on with the reagent. At the point of separation of the fluids a whitish ring is formed, owing to precipitation of the proteins by the trichloracetic acid. If the ring remains homogeneous and disappears gradually within four or five hours, the reaction is considered negative. In a positive reaction the ring may assume the aspect of a spider's web, which fluctuates in a direction parallel to the major axis of the test tube, and which precipitates to the bottom of the tube within the first three hours. At other times the ring remains adherent for several hours to the walls of the test tube. Again, a more or less dense coagulum, irregular in its margin, is formed and gradually reaches the bottom of the test tube. The reading should be made between the second and third hour after the contact of the reagent with the cerebrospinal fluid.

With the technic described, Pacifico investigated more than 150 specimens of cerebrospinal fluid; he arrived at the following conclusions: 1. The Taccone reaction is technically simple, the reagents are stable, reading is easy and there is marked sensitiveness. 2. The determination of a positive reaction is probably not influenced by the presence in the fluid of oxidizing substances or ferments, but is related to an increase in protein substances in general. The action of the bichromate is limited presumably to hardening of the proteins which are precipitated by the trichloracetic acid. 3. The appearance of a positive reaction (fluctuating ring) and of the so-called encephalitic reaction (adherent ring) in cerebrospinal fluid containing normal protein discloses a slight increase of globulin (as low as 6 or 8 cg). This slight change, which the Taccone reaction reveals, is below the threshold of sensitivity for other common tests for globulin (Pandy, Nonne-Apelt and Weichbrodt reactions).

The sensitivity of the reaction makes it particularly available in furnishing the first indication of an initial biochemical modification of the cerebrospinal fluid and therefore constitutes an element of value for diagnosis and prognosis in indicating the existence of an organic condition. The reaction is not characteristic of any particular disease and is helpful only in establishing the existence of involvement of the nervous system.

FERRARO, New York.

ACUTE NECROTIC MYELITIS. G. MARINESCO and ST. DRAGANESCO, Ann. de méd. **31**:1, 1932.

Foix and Alajouanine, in 1926, published two cases of *myélite nécrotique subaiguë*. They were characterized by a spastic paraplegia with amyotrophy, which gradually changed to the flaccid type and then was combined with thermoanesthesia and analgesia. The spinal fluid contained an excess of albumin and a moderate number of lymphocytes. The anatomic substratum was a diffuse myelopathy with the formation of multiple necrotic foci, mostly in the gray matter. Mesarteritis and endarteritis of the meningeal and spinal vessels were also found. Other similar cases have since been reported by van Bogaert, van Gehuchten, Lhermitte and Minea.

The two cases which are added by the authors are of an acute type, lasting five and three weeks, respectively. The first, in a woman, aged 47, with fourteen births, among which were six miscarriages, began with violent pains in the back, followed two weeks later by a flaccid tetraplegia with retention of urine. Sensation for temperature and pain was markedly diminished; tactile and deep sensibility were not disturbed. Cystitis and pyelonephritis developed. Histologic examination of the spinal cord revealed necrotic areas in the anterior horns of the lower cervical segments filled with the débris of nerve fibers and a few gitter cells. Scattered throughout the white matter there were areas of spongy necrosis, with marked

swelling of nerve fibers and the formation of scattered compound granular corpuscles. Arteritis was absent, and only in the medulla oblongata was a mild perivascular round cell infiltration found.

The second case was that of an engineer, aged 52, who succumbed twenty days after the sudden onset of a flaccid paraplegia, to which later were added analgesia and thermanesthesia, with a level at the seventh dorsal segment. Retention of urine and a mild rise in temperature began on the third day. The spinal fluid contained 1.6 Gm. per thousand cubic centimeters of albumin and 3 cells per cubic millimeter. At autopsy a softening of the anterior half of the spinal cord between the fifth and the seventh dorsal segment was found, together with a thickening of the pia-arachnoid surrounding the cavity. There was a marked lymphocytic perivascular infiltration, together with a spongy necrosis in the preserved white matter. In this case, too, endarteritis and mesarteritis were absent—an important feature, which differentiated both cases from those reported by Foix and Alajouanine.

WEIL, Chicago.

THE YEARS OF PUBERTY IN A PUBLIC SCHOOL. ROBERT SAUDEK, Character & Personality **1**:17 (Sept.) 1932.

The idea that intelligent children have an inferior handwriting does not stand the test of statistics; nor does lack of speech necessarily impair or improve the calligraphy. Indeed, legibility of handwriting depends as much on the reader as on the writer. It is, for example, much more difficult to recognize the letters in a note written in a foreign language than in a note written in one's native tongue. What makes handwriting legible is not so much its beauty as its consistency. A purely conventional, handsome calligraphy often reflects a mind too dull to find other means of expression and consequently obliged to employ the mechanically learned rules.

To illustrate the value of examination of handwriting, Saudek reports a study of 131 letters written by a student in an English public school between the ages of 8 and 15. Because of the natural shyness of many boys of this sort, the letters are concerned with more or less indifferent topics, notably school athletics, rather than with subjects of emotional importance to the writer. This is true in the case under study, and the modal changes occurring in the boy's personality during the seven years must be inferred from changes in the handwriting, rather than from the content of his letters. At first the letters showed a lack of concentration, an erraticism and a fidgetiness which one would naturally expect to trouble a child of 8 in his first year away from home. At the age of 11, the calligraphy suddenly deteriorated and displayed omissions, perseverations and anticipations. This was a reflection of an irritation unhappiness—a deep dissatisfaction with life in the dormitory and in public school. Within a year marked improvement had occurred. The tremulousness, the variability in style and the anticipations of the previous samples had vanished. Accompanying this was an improvement in the boy's state of mind—an increase in confidence and a growing satisfaction, or at least an understanding, of his difficulties. At about the age of 15, the content of the letters became interesting. Into them he poured the stream of his emotions. Within a few months this changed, and the letters became routinized and showed evidence of a pretended carelessness in the concealing of these emotions.

The paper is illustrated by photostatic fragments of the handwriting.

DAVIDSON, Newark, N. J.

BLOOD SUPPLY OF THE GLIOMAS: ITS RELATION TO TUMOR GROWTH AND ITS SURGICAL SIGNIFICANCE. C. A. ELSBERG and C. C. HARE, Bull. Neurol. Inst., New York **2**:210 (July) 1932.

The authors studied the number and situation of the blood vessels in different histologic types of gliomas. Macroscopic and microscopic studies were carried out on 50 gliomatous brains, in which the following types of tumors occurred: glioblastoma multiforme, 24; astrocytoma, 15; medulloblastoma, 9; oligodendro-

glioma, 1; ganglioneuroma, 1. The sections were cut so as to contain the central and peripheral tumor tissue and the adjacent normal brain substance. In the microscopic studies the number of arteries in each field was counted from one end of the specimen to the other and from side to side. Both gross and microscopic examination showed striking differences between the numbers of blood vessels in the central and peripheral parts of the tumor and in the adjacent brain tissue.

In the astrocytomas and the medulloblastomas, the largest number of vessels occur in the central parts of the growths, and there is no increase in the number of arteries in the adjacent white matter. In glioblastoma multiforme, the peripheral areas of the tumor contain the largest number of arteries, and the vessels in the adjacent brain tissue are definitely increased.

The authors assume that there is a close relationship between the blood supply and active tumor growth. They interpret the differences in blood supply and manner of invasion of brain tissues by astrocytoma and medulloblastoma, on the one hand, and of glioblastoma multiforme, on the other, as expressions of differences in degree of malignancy; the "active" infiltration, in the case of glioblastoma multiforme, by peripheral rather than central growth, signifies its greater malignancy.

The difference between the blood supply of astrocytoma and medulloblastoma and glioblastoma multiforme can be recognized at operation. In removing these growths, the authors first bisect the tumor. This permits a better orientation concerning the size and removability of the growth. If the tumor is an astrocytoma or a medulloblastoma, the most actively growing central portion is first removed. In glioblastoma multiforme the attack is directed to the peripheral portion of the growth.

KUBITSCHEK, St. Louis.

JUVENILE CEREBROVASCULAR DISEASE. ERICH KATZENSTEIN, Schweiz. Arch. f. Neurol. u. Psychiat. **28**:237, 1932.

Katzenstein presents the results of a careful anatomic study of the brain of a woman, aged 28, who died after a cerebral hemorrhage. Ten years prior to death she had had a similar accident, which was followed by aphasia and right hemiparesis, which were transient, and right hemianopia, which regressed until the visual defect was confined chiefly to the lower quadrants. At autopsy, the calvarium was asymmetrical, and an extensive left subdural hematoma communicated through a rupture in the cortex with a large clot in the substance of the temporal lobe. In the region of the inferior horn of the left lateral ventricle and medial to the fresh clot lay the residue of the previous hemorrhage in the form of a small cyst. A few small hemorrhages of recent origin were present in the brain stem. Stained serial sections revealed degeneration of the vertical and horizontal limbs of the optic radiation, extending back to the region of the calcarine fissure in the retroventricular portion of the occipital lobe. Anteriorly, changes in the ependymal and subependymal tissues permitted the conjecture that the older hemorrhage had ruptured into the ventricle. The dorsomedial part of the left external geniculate body was degenerated. The caudal portions of the choroid plexuses of both lateral ventricles contained many hyaline bodies and showed proliferative changes in the blood vessels and connective tissue. These changes were marked on the left, where relics of a previous hemorrhage into the plexus were discovered.

Although the patient's vascular system presented no other anomalies, the changes in the choroid plexus prompted the belief that the posterior branch of the sylvian artery, which ruptured, had previously been altered in some manner. The author also expresses the opinion that emotional disturbances might have served not only to precipitate the first accident but also to have contributed to the development of the foregoing vascular changes. Representation of the various parts of the retina in the external geniculate body and optic radiation are considered in some detail. The relative preservation of vision in the right upper quadrants of the fields in the face of an extensive degeneration in the left optic

radiation seemed to support the belief that fibers conveying impressions from the lower quadrants of the retina extend far out into the white matter of the temporal lobe.

DANIELS, Rochester, Minn.

IMMUNITY TO POLIOMYELITIS IN GENERAL POPULATION: PROBABLE MECHANISM OF PRODUCTION. S. D. KRAMER, J. A. M. A. **99**:1048 (Sept. 24) 1932.

According to Kramer, immunity to poliomyelitis, as indicated by neutralization tests, has been shown to be widespread. A notion of the mechanism through which it comes about may be gained from a consideration of the rapidity with which it develops in reference to age and concentration of population. Infants born of immune mothers are immune to poliomyelitis for at least the early months of life. The age distribution of the disease and neutralization tests show that this immunity is lost by the end of the first year. The age distribution further indicates an increasing immunity in the population with increasing age. Neutralization tests on persons of different ages have shown that nine tenths of urban persons become immune by the time adult life is reached. The marked discrepancy between the amount of immunity to poliomyelitis in urban and in rural populations suggests that its extent and rapidity of development are related to the concentration of population in direct ratio to the opportunities for contact. The mechanism involved in the immunization against certain other diseases is readily understood. In measles, for example, immunity is conferred only through an attack of the disease: In the course of a lifetime, the majority of persons have measles. With diphtheria, the source of a similarly widespread immunity is not so obvious, but Schick tests show that most persons acquire immunity to the disease without having a recognized attack. This widespread immunization is accounted for by a carrier rate sufficient to "saturate" the population in the course of the first twenty years of life. The author presents evidence which indicates that immunity may follow exposure to the virus without evidence of disease. Furthermore, he suggests an explanation for the widespread immunity to poliomyelitis similar in mechanism and extent to that of diphtheria. It would seem, however, that further search for the underlying factors that determine the outcome of exposure to the virus in the two types of persons, immunity in one and disease in the other, might more nearly approach the solution of the problem, the control of poliomyelitis.

EDITOR'S ABSTRACT.

DIAGNOSIS OF EARLY POLIOMYELITIS. J. E. GORDON, J. A. M. A. **99**:1043 (Sept. 24) 1932.

Gordon points out that two benefits accrue from the recognition of poliomyelitis in its preparalytic period. The public health is benefited by isolation of affected persons at the earliest possible time. The second advantage is to the patient through early institution of treatment, whether it is carefully prescribed rest in bed, reduction of pressure by drainage of the cerebrospinal fluid or the use of presumably specific measures. Preparalytic poliomyelitis is a clinical entity distinguishable from similar conditions with relative surety. The facts contributing to clinical recognition have been repeatedly emphasized, and yet practical experience indicates the need for better appreciation generally of the clinical nature of early poliomyelitis. The disease is too often first recognized by the presence of paralysis. Equally unfortunate is the tendency during an epidemic to advance the diagnosis of poliomyelitis for many other and more common diseases of childhood without sufficient critical differentiation. This circumstance leads to unsatisfactory management of conditions that are not poliomyelitis, and to undue alarm about the actual prevalence of the specific infectious disease. The diagnosis of early poliomyelitis depends on a sound clinical suspicion substantiated by evidence derived from examination of the cerebrospinal fluid. Epidemiologic evidence aids diagnosis, in that cases are more numerous in August, September and October, with young children more affected than other age groups. The symptoms are those of many general infections, including typically a low grade fever, headache and vomiting. Three outstanding physical signs contribute the greatest aid. They are stiffness

of the neck, rigidity of the spine and ataxic tremor of the extremities. The diagnosis is primarily clinical. When the evidence suggests poliomyelitis and other possibilities have been eliminated, confirmation is effected by lumbar puncture at the proper time. The cerebrospinal fluid in poliomyelitis is essentially clear, rarely of greater turbidity than slight haziness. Laboratory differentation thus revolves into distinguishing infections of the central nervous system characterized by clear fluids.

EDITOR'S ABSTRACT.

THROMBO-ANGIITIS OBLITERANS: RESULTS OF SYMPATHECTOMY. ALFRED W. ADSON and GEORGE E. BROWN, J. A. M. A. **99**:529 (Aug. 13) 1932.

Adson and Brown report that their experiences with sympathetic ganglionectomy and trunk resection in the treatment of Raynaud's disease due to vasomotor spasm of peripheral arteries led them to employ the same surgical procedure in thrombo-angiitis obliterans, when vasomotor spasm was a contributing factor in the production of symptoms. They consider that the real problem in thrombo-angiitis obliterans is to select suitable cases for operation and to decide when operation is indicated. It is obvious that vasodilatation cannot be produced in an arteriosclerotic or occluded artery, and that surgical intervention is useless unless there is positive evidence of vasospasm in the remaining nonoccluded arteries. The operation is not indicated in the milder cases or in those in which response is quick and favorable to medical treatment. In advanced cases of massive gangrene the condition is likewise nonsurgical unless it is hoped to effect a lower amputation than otherwise would be required. Following amputation, sympathectomy may be indicated to preserve the opposite extremity. The operation has proved to be of greatest value in slowly progressive cases and in those in which patients cannot afford or are unable to sacrifice the time required to rest in bed and receive local heat, contrast baths and vaccine therapy. The authors present a review of a hundred consecutive cases of thrombo-angiitis obliterans in which they performed ganglionectomy. There were eighty-nine bilateral lumbar sympathetic ganglionectomies and trunk resections and fifteen bilateral cervicothoracic ganglionectomies with resection of the upper portion of the thoracic trunk. Operation was performed in four cases of thrombo-angiitis obliterans involving both the upper and the lower extremities, which accounts for one hundred and four bilateral operations. Ninety-six patients were males and four were females. The condition of eighty-seven of the patients was improved by the operation. The average degree of improvement was 80 per cent.

EDITOR'S ABSTRACT.

SCHIZOPHRENIA: CLINICAL FORMS. I. CUNHA LOPES and H. PÉRES, An. assist. a psicop., 1931, p. 89.

Lopes and Péres describe the various conceptions of schizophrenia that have existed since Pinel (1809), Esquirol (1814) and Spurzheim (1818) described under different names unquestionable cases of this disease, which later, in 1858, Morel termed "dementia praecox." They mention the works of many psychiatrists who studied the various syndromes of schizophrenia from Kahlbaum (1863), Kraepelin (1893) and Bleuler (1911) down to Bumke (1924) and H. de Jong and Baruk (1930). Following Kraepelin, they divide psychoses found represented in the Hospital Nacional and the Instituto de Psicopatologia, taking as a basis the evolution and the mental structure, into two large classes: (1) morbid processes beginning at a determined time which are incurable and lead to a permanent transformation of the personality, and (2) abnormal phases of reaction that are transitory and curable, which are revealed as variations of the individual disposition. The first class includes schizophrenia, and the second class manic-depressive psychoses and other types. The four subclasses of the first class that are sufficiently distinct to justify a special term are: (1) heboidophrenia, (2) hebephrenia, (3) catatonia and (4) dementia paranoides. The authors give short histories of three cases of heboidophrenia, seventy-four cases of hebephrenia, fifty-one cases of catatonia and eighteen cases of dementia paranoides. They give a table showing the age incidence

of schizophrenia in the 147 patients (men and women) found in the two institutions named. The highest representation (26.5 per cent) was in the 21 to 25 year age group, and the second highest (20.4 per cent) in the 26 to 30 year age group. A second table shows the relative incidence of the four main types of the first class of psychoses. Hebephrenia had the highest incidence, catatonia was second, dementia paranoides was third and heboidophrenia was fourth. Of 970 patients in the Brazil psychopathic hospitals, they found 147 to be schizophrenic.

EDITOR'S ABSTRACT.

EXPERIMENTAL MULTIPLE SCLEROSIS IN DOGS FROM INJECTION OF TETANUS TOXIN. TRACY J. PUTNAM, JOHN B. MCKENNA and JOSEPH EVANS, J. f. Psychol. u. Neurol. **44**:460, 1932.

In 1897, Claude observed that in one of several dogs inoculated repeatedly with minimal doses of tetanus toxin ataxia and spasticity of the limbs developed, and it died about two months later. Necropsy revealed scattered islets of sclerotic tissue throughout the central nervous system. Histologically, this tissue consisted of a cellular exudate (vascular and glial) and demyelinization. Ceni and Besta found similar lesions in one of several animals inoculated intraperitoneally with Aspergillus fumigatus. The animal was killed three months after the onset of the symptoms, and the lesions were found to resemble those described as "acute multiple sclerosis," disseminated encephalomyelitis and disseminated degenerative softening in man. Similar observations were reported by Perdrau and Pugh in four of fourteen dogs affected with the "nervous form of distemper"; three other dogs showed areas of perivascular infiltration without demyelinization. For the last three years, Putnam, McKenna and Evans have attempted to reproduce Claude's and Ceni and Besta's experiments. No nerve lesions were found in dogs inoculated with Aspergillus spores or extract. Of about 80 dogs inoculated with tetanus toxin in doses similar to those employed by Claude, two have shown disseminated encephalomyelitis at necropsy. In the first dog, which died thirty-five days after the first inoculation, acute disseminated lesions were found; they consisted of a perivascular infiltration, with localized destruction of myelin and relative preservation of the axis cylinders. The pathologic process also involved the optic chiasm. In the second dog, killed a year after the onset of the symptoms, similar lesions were present, but they were more chronic. In some of them the loss of myelin persisted, and gliosis was conspicuous. Histologically, the lesions resembled those observed in some cases of multiple sclerosis in man. KESCHNER, New York.

RAYNAUD'S DISEASE: A CRITICAL REVIEW OF MINIMAL REQUISITES FOR DIAGNOSIS. EDGAR V. ALLEN and GEORGE E. BROWN, Am. J. M. Sc. **183**: 187 (Feb.) 1932.

The authors review Raynaud's original work in a critical, scientific manner, in order to determine his allegiance to his criteria and to discover whether his concept is valid. The main dicta from Raynaud are: the occurrence of gangrene without arterial occlusion; the symmetry of gangrene; the occurrence of local syncope, local asphyxia and localized rubor; the type and occurrence of gangrene, and the intermittence of attacks of color changes. In a critical review of thirty-one cases that Raynaud presented, only six are acceptable as conforming to his tenets; interestingly, these six were personally observed by Raynaud. In 45 per cent of his cases, the state of pulsations in the peripheral arteries was not mentioned; in 53 per cent intermittent changes in color were not exhibited. Thus, many of Raynaud's reported cases were not illustrative of the condition described by him and, being used as models, have given rise to confusion and errors in diagnosis.

It is shown how loosely the term Raynaud's disease has been applied in a study of twenty-five unselected cases in men or children, in the lack of strict criteria. From the one hundred and fifty carefully studied cases, the authors

conclude that there is a definite primary disease or disturbance which can be called Raynaud's disease. The minimal requirements for diagnosis are those originally stated by Raynaud: (1) intermittent attacks of discoloration of extremities; (2) absence of evidence of organic arterial occlusion; (3) symmetrical or bilateral distribution and (4) trophic changes, when present, limited to the skin and never consisting of gross gangrene. Primary disease that may cause vasospastic symptoms must be excluded. Studies of this type are highly to be commended and stimulated.

MICHAELS, Boston.

LOSS OF THE MOVEMENTS OF DEXTERITY IN A CASE OF LESION OF THE LEFT PARIETO-OCCIPITAL LOBE. D. NOICA, Encéphale **27**:27 (Jan.) 1932.

Cases have been reported by Claude and Lhermitte and by Foix and Thévenard in which, as a result of lesions of the paracentral lobule, a syndrome superficially similar to a cerebellar one is developed. André-Thomas also has occupied himself with this question. The author reports the case of a man, aged 29, who was referred for neuralgic pains of the left parieto-occipital region after the extraction of a molar tooth. Presently, an abscess in the scalp in this region was discovered. Eventually a portion of the occipital bone was removed, disclosing invasion of the purulent inflammation to a depth of 1 cm. in the cortical tissue. With neurologic tests there appeared to be no true paralysis, but nevertheless there was inability to make many movements. When the finger-to-nose test was executed rapidly, the finger would go beyond its goal; when the test was made slowly and with attention it would stop short. In general, there were found dysmetria, dysdiadokokinesis and dyssynergy, without any apparent cerebellar lesion. There were no disturbance of equilibrium, no nystagmus, negative Bárány tests, and no history to point in any way to the cerebellum. Then, too, on movements with the arms, for instance, the patient followed his movements with his eyes — which is not usual in a case of cerebellar disturbance. Many characteristics of the movements are described, indicating wherein they vary from true cerebellar signs. Examination on the following day showed some remarkable changes. Whereas on the previous day he could perform certain movements badly or not at all, he could now repeat them effectively. This could not be reconciled with a cerebellar basis — if the movements were dyssynergic they would certainly improve slowly. But it was the sense of *how* to perform a technical movement once known that was lost — not any of the movements themselves. When the patient was given instruction, and observed the movements, he readily "got the hang of the thing" and was able to reintroduce his previous dexterity. In other words, he had lost the idea of the movements which he had learned in infancy under visual control, and now, under visual direction, could rapidly relearn the movement.

ANDERSON, Los Angeles.

ROTATORY FORM OF OPTOKINETIC NYSTAGMUS: PHYSIOLOGIC DEDUCTIONS. RAOUL CAUSSÉ, Rev. d'oto-neuro-opht. **10**:100 (Feb.) 1932.

Ocular movements in the normal man may be divided into: voluntary (active optic fixation), passive optic (optokinetic reflex) and passive vestibular (labyrinthine reflexes). In previous investigations of this question only the longitudinal form of optic movement (elevation, depression and lateral movements) and convergence have been studied. Rotatory movements around the anteroposterior axis have received little attention, although their great importance from the vestibular standpoint is manifest. While labyrinthine influences can produce rotatory nystagmus or ocular counter-rolling, it is not possible voluntarily to rotate the eye around the anteroposterior axes. With the technic of Borries it is possible to obtain passive optic rotatory movements, but they differ from other forms of optokinetic reactions in that they are inconstant, slow and of short duration; accommodation suppresses them and the law of Bárány that optic nystagmus always overcomes vestibular nystagmus is in default. Therefore, the conclusion is justified that "longitudinal movements are essentially under the optic influence

(active and passive), which largely overcomes the vestibular influence. Rotatory movements, movements strictly reflex, are almost exclusively dependent on the vestibular apparatus."

In the lower vertebrates, ocular movements are exclusively commanded by the labyrinth. In the course of evolution and with the development of cerebral function, passive, then active, ocular motility independent of the labyrinth becomes possible. In man this divorce is complete; in fact, the eye supplements the vestibular function. Nevertheless, in the function of rotatory motility of the globe, the ancestral servitude of the eye to the labyrinth is marked.

DENNIS, Colorado Springs.

A CONTRIBUTION TO THE KNOWLEDGE OF THE CORTICAL CHANGES IN PUERPERAL ECLAMPSIA. WALTER BENOIT, Ztschr. f. d. ges. Neurol. u. Psychiat. **131**:602 (Jan.) 1931.

Benoit reports the case of a woman who, after giving birth to a premature child at 8 months, developed generalized convulsions, hypertension and delirium. She died in seventeen days. Necropsy showed pneumonia in both lungs, a puerperal uterus and a fatty liver. The brain changes were varied, but could all be traced to the results of vascular (arterial) spasm. In one area on either side of a sulcus was an area of softening with edematous meninges, gliosis, disappearance of the ganglion cells, and an increase in microglia cells toward the softened side of the cortex. Besides softenings of this sort, the cortex showed incomplete necroses usually following along the course of the vessels. The latter showed swollen endothelium. Deep in the white matter, glial scars were found, and in Wright preparations a status spongiosus. Areas of pallor were also found. The cerebellum was the seat of softenings, and the Purkinje cells showed the homogeneous changes described by Spielmeyer. Gliosis was present in the dentate nucleus. Benoit attributes the changes to vascular spasm.

ALPERS, Philadelphia.

THE ANATOMIC BASIS OF SLEEP. V. E. MICHEEV, J. nevropat. i psikhiat. **1**:75, 1931.

Five cases of brain tumor were reported in which sleepiness was the most prominent feature. In all the cases at autopsy there were tumors in the vicinity of the fourth ventricle. Of course, tumors frequently cause somnambulance in patients as a result of the increase in intracranial pressure, but even a slight involvement in the region of the fourth ventricle causes disturbances in sleep. The author believes that sleep is regulated by a rather large area extending from the fourth ventricle to the optic thalamus. He discusses the various theories of sleep, especially those advanced by Pavlov and his school. He cites an extremely interesting experiment of Krilov, who was able to induce deep sleep in a dog by the administration of chloral hydrate through a rectal tube. After the dog had been accustomed to the experiment the mere preparation for the procedure induced sleep. Injections of warm water also produced sleep. The author believes that sleep is a function of the organism as a whole, with the midbrain acting as a regulator of sleep and of wakefulness.

KASANIN, Howard, R. I.

THE REFLEX OF POSTURE OF THE BICEPS. H. CLAUDE, H. BARUK and S. NOËL, Encéphale **26**:581 (Sept.-Oct.) 1931.

On the basis of electromyography and other studies, the authors come to the following conclusions: First, there are two orders of muscular reaction typified by the biceps; one of these is the reflex of true posture; the other is a psychomotor muscular reaction which varies according to the state of psychologic tension and can in many cases mask the true posture reflex. Second, these two types of reflex have clinical, graphic and electromyographic characteristics that enable

them to be differentiated. Their diagnostic value also is very different. The first type, that is, reflex posture, is probably best observed in cases of parkinsonism. The other is seen at a maximum in catatonia. Third, each of these two orders of reaction has its corresponding cerebral substrate, and, depending on the focus of damage within the brain, signs are produced either alone or together rendering clinical differentiation possible.

ANDERSON, Los Angeles.

OBSERVATIONS ON REFLEX ACTIVITY AND TONICITY IN ACUTE DECAPITATE PREPARATIONS, WITH AND WITHOUT EPHEDRINE. J. C. HINSEY, S. W. RANSON and F. R. ZEISS, J. Comp. Neurol. **53**:401 (Dec.) 1931.

Thirty adult dogs of medium size, divided into two groups, were used. Twenty were given ephedrine, and ten were not. The authors describe in full their procedure for decapitation, which makes possible the control of hemorrhage and of the level of transection. Ephedrine was administered through the external jugular vein. Administration of ephedrine to decapitated dogs facilitated the development of an extreme degree of resistance to passive flexion in the limbs. They found that if the animals are properly balanced on their hind limbs, they will stand and support their body weight for considerable periods. The animals were more active reflexly after the injection of ephedrine. They conclude that the mechanism for standing is present in the decapitate dog as well as in the chronic spinal preparation, and that removal of effect of shock makes possible its demonstration.

ADDISON, Philadelphia.

OCULOGYRIC CRISES AND PARKINSONISM IN CEREBROSPINAL SYPHILIS. KNUD H. KRABBE, Acta psychiat. et neurol. **6**:457, 1931.

Krabbe discusses whether, in a patient who has syphilis and presents a clinical syndrome characteristic of epidemic encephalitis, the symptom complex is due to the encephalitis or to the syphilis. He reports five cases. The first case, one of parkinsonism in a patient with long-standing syphilis, he considers to be true Parkinson's disease. The second, a case of progressive parkinsonism following an attack of influenza in a syphilitic person, he regards as epidemic encephalitis. In the third, a case of typical chronic encephalitis in which syphilis developed while the patient was under observation, he thinks that perhaps the syphilis aggravated the encephalitis. The fourth case he considers as epidemic encephalitis complicated by syphilis. The fifth case showed serologic evidence of cerebral syphilis, and the symptoms were improved by treatment; this case he believes was syphilitic parkinsonism, and concludes that syphilis alone probably can produce the parkinsonian syndrome.

PEARSON, Philadelphia.

PSYCHOSES ASSOCIATED WITH SPRUE. A. U. VIJASNOVSKY, J. nevropat. i psikhiat. **1**:35, 1931.

Sprue is endemic in the Far East. In 1923, A. Kriukov described the first case of this disease in Central Asia. Since then, fifty cases have been reported. The author describes six cases of sprue, with a psychosis developing during the course of the disease. The mental symptoms may develop early or late in the illness. The clinical picture is usually characterized by a delirium with hallucinations. The development of a psychosis carries with it a grave prognosis for life. In the cases described by the author, there was either a positive heredity of mental disease or else a definitely inadequate personality. In women, the psychosis develops in the period of lactation or the menopause. Autopsies in the cases show lesions, not only in the internal organs but also in the central nervous system. The changes in the brain are those usually found in other toxemias, passing through the hemato-encephalic barrier of the brain.

KASANIN, Howard, R. I.

SURFACE TENSION OF SERUM IN GENERAL PARALYSIS. B. H. SHAW, Brit. M. J. **1**:623 (April 11) 1931.

The author reports the following test for dementia paralytica. To 50 cc. of distilled water is added 0.25 cc. of serum. Thorough mixture must be insured. A small platinum ring (about 1 cm. in diameter, 0.0076 wire) is suspended by a light thread from a torsion balance so that it is allowed to float on the surface of the fluid. The reading in milligrams just necessary to make the ring part company with the fluid, less the weight of the platinum attachment, gives an accurate measure of the surface tension. If now the serum is inactivated at 56 F. for thirty minutes, there is a change in the surface tension. In conditions other than dementia paralytica, the surface tension is thereby raised, or at any rate it shows no definite lowering. In dementia paralytica it is definitely lowered.

FERGUSON, Niagara Falls, N. Y.

CONCERNING THE SYNDROME ACCOMPANYING LESIONS OF THE CORPUS HYPOTHALAMICUM (CORPUS SUBTHALAMICUM) OF LUYS. V. HAKON SJOGREN, Acta psychiat. et neurol. **6**:301, 1931.

The author presents a clinical study of three cases of hemiballism with hypotonia. In the three patients there was a pronounced hypotonia in the limbs, showing hyperkenesia. In two patients the fingers and toes presented athetoid movements. The movements diminished when the patients' attention was distracted from them and ceased during sleep, but increased when attention was drawn to them. There were no vasovegetative disorders. In all the cases the prognosis regarding life was good, and in this respect these cases differed from those usually reported. Sjogren concludes that the presence of hemiballism indicates a localized lesion in the body of Luys, and would designate such cases as "the syndrome of the corpus luysii."

PEARSON, Philadelphia.

HYPERNEPHROMA-METASTASIS OR SARCOMA (?) OF THE ARACHNOID. MIKIO MURATA, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **33**:165, 1931.

Murata reports under this title a case of hypernephroma with one extensive metastasis in the brain, in a man, aged 31. The cerebral tissue surrounding the metastatic neoplasm was unusually soft and edematous. The primary tumor in the kidney was much smaller than the metastasis in the brain, which appeared pseudo-acinous, very vascular and adherent to the dura. No metastatic deposits were found in other parts of the body. The author comments on the unusual clinical as well as pathologic features of the case. Ordinarily, the characteristics of a metastasizing hypernephroma are: (1) metastases to the bones, (2) apoplectiform onset with jacksonian convulsions and (3) a relatively short duration of the disease. This case had neither of these features, and it was only the histologic appearance of the tumor that established the final diagnosis.

KESCHNER, New York.

PROGRESSIVE HYPERTROPHIC POLYNEURITIS. W. GORDON SEARS, J. Neurol. & Psychopath. **12**:137 (Oct.) 1931.

Three cases of this rare disease are recorded in a family in which there is a history of similar deformed feet in the grandfather, father, sister and her son, making seven cases altogether. Only two of the three cases presented palpable nerves, one of which was studied after biopsy; it showed marked thickening of the perineurium and endoneurium, characteristic of hypertrophic interstitial neuritis. The author describes the essential features of the disease and its differentiation from Friedreich's disease and the peroneal form of progressive muscular atrophy which it closely resembles. He does not subscribe to the opinion that the disease is merely a variety of the peroneal type of progressive muscular atrophy, but considers it a separate entity.

SPERLING, Philadelphia.

PROGNOSIS IN CASES OF INVOLUTIONAL DEPRESSION AND ALLIED MENTAL DISEASES. E. JACOBI, Arch. f. Psychiat. **95**:423 (Oct.) 1931.

The outcome of involutional psychoses in the cases of 53 persons admitted to the hospital during two years was studied; the results were: More than half of the cases had a poor prognosis; only a few could be regarded as ending in complete recovery. In the paranoid forms that occur in the fourth, fifth and sixth decades, there is a fairly frequent partial improvement. Schizophrenias that occur at this age have the poorest prognosis. In some cases that started as depressions there was, during the progress of the disease, a change into a schizophrenia-like picture with a poor prognosis. Psychogenic reactive depressions at this age tend to progressive development and have a poor prognosis. MALAMUD, Iowa City.

CHIASMATIC SYNDROME: ROENTGEN RAY THERAPY: AGGRAVATION: RECOVERY THROUGH EXCISION OF THE TUMOR. A. ROCHON-DUVIGNEAUD, P. VEIL and CHAFIR, Ann. d'ocul. **168**:931 (Nov.) 1931.

The case is reported of a man, aged 22, who for eight months had suffered from rapid reduction of visual acuity in the left eye and contraction of the temporal field. The sella turcica was very large, and the adiposogenital syndrome was present. After twenty treatments with roentgen rays the vision was unchanged. The pituitary tumor was excised on March 21. On June 11, vision was 10/10 in the right eye and 3/10 in the left eye. There was only a slight contraction of the temporal field in the right eye, and the field in the left eye was normal The pathologic diagnosis was an adenoma of the pituitary body.

BERENS, New York.

THE EFFECT OF THE STIMULATION OF ONE CARDIAC NERVE DEPENDS ON THE TONIC EXCITEMENT OF THE OTHER CARDIAC NERVES. C. L. HOU and E. T. BRUECKE, Arch. f. d. ges. Physiol. **227**:239, 1931.

After the severance of one vagosympathetic, the threshold of the opposite vagus is lowered owing to an increase of the irritability of the heart muscle; especially the "vagus substance" has now a stronger influence on the heart. This is shown by the fact that the action of acetylcholine on the heart is increased after a bilateral section of the vagosympathetic. If one cuts the accelerans alone one can observe the same effect on the excitability of the heart muscle.

SPIEGEL, Philadelphia.

BIOCHEMICAL MODIFICATIONS IN THE COURSE OF EMOTIONAL CHANGES. H. JANKOWSKA, Encéphale **26**:204 (March) 1931.

In a study of patients showing increased emotional activity certain urinary chemistry findings are reported. There tends to be an increase in alkalinity, in the total nitrogen, in time volume output, and sometimes also in calcium and ammonia. In a case of long-standing anxiety these increased figures persisted during all the stay in the hospital. In schizophrenia the same general type of urinary changes were found, even though no outward emotional changes were observed. Might this not be evidence of schizophrenia as a fundamentally affective psychosis?

ANDERSON, Los Angeles.

SUBOCCIPITAL PUNCTURE OF A CEREBELLAR CYST. BERTIL SJOVALL, Acta psychiat. et neurol. **6**:645, 1931.

Sjovall reports a case of cerebellar cyst in which the diagnosis was confirmed by inflating the cyst with air by suboccipital puncture. He believes that it is possible to use this method in other cases and states that studies on the cadaver have convinced him of its practicability, although it is associated with a certain degree of risk.

PEARSON, Philadelphia.

Society Transactions

NEW YORK NEUROLOGICAL SOCIETY AND SECTION OF NEUROLOGY AND PSYCHIATRY, NEW YORK ACADEMY OF MEDICINE

Joint Meeting, Nov. 1, 1932

HENRY ALSOP RILEY, M.D., *President, in the Chair*

CLINICAL EXAMPLES OF THE EXPRESSION OF INSTINCTUAL CONFLICTS THROUGH SYMPTOMS AND SPEECH. DR. LAWRENCE S. KUBIE.

Deep-seated bodily cravings exist in childhood before and during the period of language formation. As language develops, the child seeks to use words and to talk about these cravings and the parts of the body, or the products of the body, which are associated with them. It is striking and perplexing that even when the child has been taught the appropriate words, he frequently uses an indirect and "symbolic" form of representation. Many examples were given of the speech and behavior of normal children between the ages of 3 and 8 years. These examples were presented with exact reproduction of the words used by the child and by the adult, and with simple and accurate description of the conduct of the child. They were not complicated by any adult interpretation or stimulus to fantasy by the child. In addition to the material drawn from children, a few samples were given of self-revealing dream or disturbances of behavior in sleep, during analysis and under anesthesia.

The material presented proved that the child spontaneously represents the parts of the body frequently in one of two fundamental ways: First, there was a whole group of representative objects which were drawn from the external world, and in which parts of the body were represented as though they were independent living forms or objects. Thus one found cannon, scissors, mice, snakes, aeroplanes, buildings, machinery and other objects used for this purpose. It was pointed out that this phenomenon is closely linked to the whole process of projection, and to mechanisms of externalization of internal problems. Second, there was a form of representation in which one part of the body was substituted for another part. Under certain conditions it was observed that relatively neutral parts were substituted for those more directly involved in the instinctual craving. However, the opposite phenomenon also occurred; hence it can be seen that the translation may occur either toward the instinctual zone or away from it. Furthermore, it is clear that in this translation of experience and feeling from one part of the body to another, one approaches closely the problems of anxiety, hysteria and hypochondriasis.

The extraordinary extent to which the use of symbolic speech occurs in childhood offers significant evidence in support of the psychoanalytic interpretation of dreams and symptoms. Obviously, however, the phenomenon must be studied with rigid control of the influence of suggestion. It seems that verbal and conceptual images are ill-defined and overlapping units in the early stages of language formation. With increasing maturity these units narrow down to the circumscribed and precise elements of adult speech and thinking. In the background, however, behind the precise adult use, the more vague conceptions of childhood persist, coloring the speech, the behavior and the dreams of the adult.

MENTAL ASPECTS OF TUMORS OF THE BRAIN IN PSYCHOTIC PATIENTS. A STUDY OF 26 VERIFIED CASES. DR. GERALD R. JAMIESON and DR. GEORGE W. HENRY.

Many attempts have been made to estimate the frequency with which mental disorders are associated with tumors of the brain. Some of the published estimates are as follows: Sterling, 40 per cent; Gianelli, 50 per cent; Schuster, from 50 to 60 per cent, and Knapp and Baruk, 75 per cent. Oppenheim, Bruns and Moersch state that mental symptoms occur in practically all cases of tumor of the brain. Such apparent discrepancies in clinical observation are readily understood when the many factors that vitiate a statistical study of this kind are taken into consideration. In fact, it is generally conceded that there is no psychosis peculiar to tumor of the brain, although certain combinations of clinical phenomena may be strongly suggestive of a new growth in the brain.

In this report are presented the clinical observations on twenty-six psychotic patients in whom tumors of the brain developed, the presence of which was established by postmortem examination. In about one third of the cases a well developed psychosis had been recorded before there was any indication of a tumor. In some cases the clinical manifestations were modified by senility, arteriosclerosis, syphilis or alcoholism, but otherwise the sole factors were the type of personality, the previous psychosis and the tumor.

The diagnoses made represented the more prominent features of the clinical picture, at least in the first part of the illness, and they indicate the difficulties with which the physician is confronted in trying to arrive at a correct diagnosis. The fact that a diagnosis of tumor of the brain was not made in more than 30 per cent of the cases before death is a stimulus to further effort in the attempt to recognize its presence.

If it were possible to describe a psychosis peculiar to tumor of the brain, this would undoubtedly have been done long ago. There are, however, certain general features in the clinical picture which are of special interest to the psychiatrist and which are illustrated by the cases presented. It is noteworthy that every psychotic patient has individual peculiarities and that any complicating physical disease produces radical changes in the clinical picture. The patient then begins to behave and talk in a more normal way, at least as long as the complicating disease forces itself on his attention. He interrupts his psychotic behavior and speech to make known that he is not feeling well, that he has a headache, that he suffers from vertigo or that he is in some other way in distress. As a rule these complaints are not associated with, or supported by, psychotic trends. In other words, there is a marked contrast between the new symptoms and those characteristic of the uncomplicated psychosis. In addition, there may be radical changes in the behavior or in the general condition of the patient, including the appearance of abnormal neurologic signs. If the manifestations of a tumor of the brain superimposed on a psychosis are to be described briefly, it may be said that they are characterized by changing contrasts and incongruities in the symptoms and signs and by evidence of organic disease of the brain which becomes increasingly obvious.

Periods of blind, impulsive excitement, frenzy and violence, with unaccountable irritability, may be followed by or alternate with periods of generalized retardation, mental dulness, somnolence or stupor. There often are intervals during which the patient returns to his former psychotic state. The somnolence may be dissipated by repeated questions or other stimuli, only to return when the patient is free to follow his own inclinations. Carelessness in personal appearance and incontinence indicate the increasing apathy.

The patient's talk is consistent with other forms of psychomotor activity. When aggressive he is often unpleasant and abusive. At other times he may have great difficulty in elaborating and expressing his thoughts, and he may even become mute. These wide variations in the degree of psychomotor activity may take place within a short period and are in striking contrast with the former clinical picture.

The mood of the patient is usually consistent with the seriousness of the illness or the degree of suffering. More than half the patients were depressed, and a

larger percentage were distinctly apprehensive. Euphoria was uncommon, and its presence was always in striking contrast to the actual situation. At least one fourth of the patients had suicidal tendencies.

Disorientation or confusion was common, especially when the tumor involved the frontal, parietal or temporal lobe. It seems rather characteristic that the amount of confusion fluctuates, apparently according to the degree of increased intracranial pressure.

Disorders of memory and retention were most directly related to the amount of confusion present. As a general rule, the more complex intellectual processes suffered first; there were times when memory and retention were almost lost. Recent memory was usually more seriously affected, and not uncommonly fabrications could be elicited.

At least one fourth of the patients had some insight into the fact that a serious complication had arisen in the illness or that mental functions had been altered. Their own spontaneous complaints should have aroused the curiosity of the physician and furnished valuable clues as to the nature of the complicating disease. Through a change in symptoms these patients gave from a few months' to several years' warning of the presence of organic disease of the brain, and when the peculiar variations in the clinical picture are considered it would seem that tumor of the brain should have been included among the possibilities.

The series of cases presented is not sufficiently large to permit many general conclusions, but the findings are essentially in agreement with those of Baruk who has made a similar study in forty-one cases of tumor of the brain verified anatomically. It is probable that the extremely irritable, anxious, excitable and aggressive periods represent distress from localized pressure or the milder degrees of increased intracranial pressure which seriously interferes with all conscious activities. In physical suffering the psychotic patient is no different from any other person. He either prefers to be left alone or appeals for help. Whenever he indicates through his complaints or behavior that the distress is within his head he speaks as loudly as he would if he were normal, and he should be heard, providing the physician is not distracted by the manifestations of the psychosis.

MENTAL DISEASE: THE NEUROLOGIST'S POINT OF VIEW. DR. I. S. WECHSLER.

At the present time, two schools of thought dominate the approach to mental diseases: one, the psychologic or psychopathologic; the other, the organic or pathophysiologic. The neurologist is therefore confronted with a dilemma. He looks on mental disorders as diseases of the nervous system and finds it difficult to discriminate between functional and organic conditions. He recognizes, of course, the interrelations among the brain, the vegetative nervous system, the glands of internal secretion and other organs, disturbances in which may express themselves in mental disease; he knows that mental disorders can occur in the absence of demonstrable pathologic lesions, and admits that emotion is capable of disturbing normal physiologic function as well as of bringing about abnormal mental reactions. He is also aware that mental disorders can result from inharmonious interaction between the individual and the group and between the individual and his environment, but he feels that, potent as environment is, heredity plays a tremendous rôle and cannot be ignored as a result of "constitution" or be altogether conjured away.

The neurologist, therefore, is confronted with this dilemma: He views mental disorders as disease entities, exactly as he views other diseases, and yet he cannot define or deal with the former in the same terms as with the latter. He must, therefore, resort to psychopathologic concepts, despite his conviction that pathophysiology holds the key to the riddle of mental disease. But the neurologist puts emphasis first and foremost on the study of the structure and function of the nervous system, for the understanding of normal and abnormal mental behavior, and insists on the use of the scientific experimental method. He is convinced that both neurology and psychiatry are intimately bound up with general medicine and that

clinical facts objectively evaluated are superior to fanciful theory. He recognizes the modest contribution of academic psychology to the understanding of mental behavior, and concedes that psychoanalysis is the most fruitful psychologic method yet devised for the study of both normal and abnormal mental reactions. He is fully aware of the importance of genetics in psychiatry as well as of the need for better understanding of instinctual and emotional reactions and of social, industrial and economic factors and for investigation of a host of ancillary problems that bear on mental disease. But he must insist on the use of accurate scientific methods in all these fields, and is not content with arm chair philosophic and pseudopsychologic speculations. He insists on the elimination from psychiatry of metaphysics and modernized scholasticism and rejects the anthropomorphization of concepts. He does not reject theory, but merely asks that it be tested by objective experience. Conceding the present difficulties and limitations of the neurologic approach, he is convinced that ultimate understanding of mental disease will come from the study of structure and function, and that psychopathology, useful and necessary as it is at the present time, merely bridges gaps which the accumulation of knowledge will ultimately fill.

MENTAL DISEASE: THE PSYCHIATRIST'S POINT OF VIEW. DR. BERNARD GLUECK.

The point of view of the psychiatrist toward mental disease may be presented by reviewing the traditional opposition between the "organicist" and the "functionalist." Mental disease is a disorder of the personality as a whole. The personality embraces all the familiar structures and integrations of functions from the fields of anatomy, physiology and biochemistry and also those higher integrations which are conditioned by the racial heritage of man and which begin to emerge with the birth of the child and with his first contacts with other human beings. These higher integrations at the psychic level not only are intended to serve the immediate adjustive requirements of man in his impacts with reality, but are engaged from birth until death in the important task of maintaining a satisfactory adjustment between two sets of forces which contend for the mastery of the person and his conduct, namely, the forces of nature or instinct and those of nurture or culture. Disease and maladjustment of the personality as a whole, from the commonplace hysterical headache to the most profound psychosis, reveal the evidence of the unsatisfactory solution of the conflict kept alive within the soul of man by these contending forces.

Thus the causes of disorders of the personality, (i. e., of mental disease) cannot be defined by reference solely to the immediate precipitating event, whether this event is a tumor of the brain or a vascular insult to the brain, on the one hand, or a frustrated love affair or some other form of frustration or privation, on the other hand. The real explanation of mental disorder lies in the universal, and what to all intents and purposes has come to be the natural, intrapsychic conflict of civilized man. The immediate precipitating event, whether it is organic, toxic or psychologic, inhibits or destroys the capacity of the self to deal adequately with this intrapsychic conflict, and the symptoms which a given disorder reflects are indicative of the specific way in which the conflict is being handled. All of this must remain unintelligible if one limits his vision to a psychology of consciousness or the conscious self and refuses to accord equal consideration to the vastly more important psychology of the "unconscious."

Intrapsychic conflict, the tensions and anxiety produced by the opposing forces within the constitution, is thus seen to be the natural destiny of man. So-called normality reflects the achievement of a satisfactory adjustment between these contending forces. That this so-called normality ordinarily goes hand in hand with somatic integrity does not signify that structural and physical health is an absolute guarantee against those failures of adjustment which are found in the field of psychopathology. Diagnosis of "functional disorders" by exclusion after a meticulous search for somatic factors leaves one disappointed; this is not an uncommon experience in the practice of neurology.

One is justified in following Freud when he says: "The meaning of a symptom lies in its connection with the life of the patient." The wish-fulfilment character of sensory falsifications, such as illusions and hallucinations, is not invalidated by the circumstance that these manifestations might be released by a toxemia or an organic encephalopathy. The compensatory or defensive character of a delusion is not disproved by the circumstance that it occurs in a patient with dementia paralytica. While the compulsion neurosis differs from hysteria in the psychologic dynamics and content which underlie these disorders, they both illustrate types of situations in which the claims of instinct have experienced an unnecessarily excessive restriction or denial in response to excessive taboos imposed on the person by the side of his nature that is influenced by culture and education. The explanation of a psychoneurosis lies not in the psychoneurotic person's friction with his environment but in the intrapsychic conflict. So far as the claims of society or culture—claims which the individual is obliged to heed almost from the moment of birth—constitute one element of this conflict, they have become absorbed and to all intents and purposes part of the nature of the individual, and have acquired a degree of significance and power approaching that held by instinct itself.

It must be clear that the point of view defended is the psychoanalytic approach to psychiatry. There is no justification for the criticism that this approach is antagonistic to scientific methods. Psychoanalysis is to traditional psychiatry what histology is to anatomy; it is an extension and refinement of the psychiatric instrument. It had its origins in an endeavor to find a more reliable means for the definition and the treatment of psychopathologic disorders. Its entire phenomenologic and conceptual structure has been built up out of clinical experience with psychopathologic disorders; when conceptual constructions have outdistanced empiricism Freud has never hesitated to say so.

The application of the psychoanalytic instrument to psychiatry naturally goes beyond mere description and prognostication on the basis of the spontaneous outcomes of certain symptom complexes. While it has stimulated a much more minute and careful observation of the manifestations of psychic disorder, it aims furthermore to discern the meaning of these revelations, the "whys" and the "wherefores" of the symptoms. It goes beyond this, and viewing disease as an endeavor, albeit an unsuccessful one, at adaptation, it postulates this question in each case: "What is the patient trying to achieve by means of his disorder?" Or, in other words, what need is the neurosis filling? That every neurosis or psychosis represents a failure of adaptation cannot be gainsaid, but it is also true that every disorder of this nature is capable of revealing the specific issues which created the problem and which the patient is endeavoring to solve by means of his disorder.

It is difficult to conceive how this type of conception of psychopathology can leave room for valid differences of opinion between the "organicist" and the "functionalist." If one were to indulge in a paradox, one might insist that the "functional" concept of the psychoanalyst "out-organicizes" the traditional organicist. For it certainly strikes more directly and more surely, and by the same token more organically, at the root of the problem of mental disease.

DISCUSSION ON PRECEDING PAPERS

DR. BERNARD SACHS: You have listened to neurologists and to psychiatrists; now listen, if you will, to a neuropsychiatrist, a term of which Dr. Hunt and I are particularly fond. I am entering this discussion seriously, the more so because I have had the privilege, the pleasure and the duty of reading the abstracts and the papers. I feel that some of the speakers are tilting against windmills. It seems to me that they have an erroneous conception of why neurologists oppose some of these doctrines. But the discussion has shown the absolute necessity and importance of bringing these subjects before this very forum. The neurologists want to have the opportunity of discussing these matters with the psychiatrists, and the psychiatrists should be equally courteous and be willing to listen to the moderate criticisms made of some of their doctrines.

The first paper presented, on the expression of instinctual conflicts through symptoms and speech, was of great interest, but it led to interpretations which might well be open to frank differences of opinion. In the interpretation of these things, there is need of free discussion. I was hoping to escape the psychoanalytic controversy, but I cannot. There are certain pillars of the psychoanalytic church; for instance, the explanation of infantile sexuality and the interpretation of the unconscious, of dreams and of the personality as a whole. On the question of personality there will be little difference of opinion, but I suggest that the society should have an evening devoted to this subject. Let various physicians, representing both neurology and psychiatry, discuss the freudian theory of dreams, the freudian theory of libido and the question of the unconscious. If these things were analyzed carefully and the arguments pro and con were presented, I think that good work would be done, and I hope that the Section of Neurology and Psychiatry will be the place in which many of these questions will be settled amicably. I have no personal feelings in this matter. I am sincerely interested in the whole controversy. The psychoanalysts must not accuse me of what they are so fond of accusing others of, viz., that I do not understand the subject. I have probably read as much psychoanalytic literature, both in the original and in translations (some of which are very poor), as any one present. Recently I picked up a little book, just republished by Freud, on the "*Vier psychoanalytische Krankengeschichten*" (Vienna, Internationaler Psychoanalytische Verlag, 1932), which contains the four rather famous histories on which much of the psychoanalytic doctrine is based. I could not help thinking of the story of the famous Hans, of which so much has been made, and which has passed into the history of psychoanalytic literature. If one will read the story one cannot help arriving at the conclusion that the story may be all right; it is the interpretation that is all wrong. Little Hans was the son of a physician and his wife (and by the way, very properly, they have been divorced since; that has been revealed only in the last edition). If one reads the story impartially, it will be noted that all the "infantile sexuality" was put into the mind of the boy in his earliest years. The parents began to talk to him about his *Wiwimacher* (the German nursery term for penis). They spoke of it to him so often that they kept his mind on it, and the boy's attention became centered on the subject. Instead of the penis being an appendage to the body, in the course of time the body became an appendage to the penis! I wish that as many as possible of the physicians present would read that history, with the purpose of determining how much inevitable infantile sexuality was present in that case, and how much was generated by the behavior of the parents. There is some comfort in knowing that after fifteen years Freud saw the boy and said that he was all right. If he is normal and remains so, it is in spite of the therapy to which he has been subjected.

Another matter to which I should like to call attention is that one does not generally get an inside view on the way in which some of the psychoanalytic therapeutic procedures work out. In a book called "Prospecting for Heaven," (New York, Viking Press, 1932) Embree, of Chicago, has attempted to imitate the dialogs of Plato, and has presented conversations between a number of distinguished men; among them, Franz Alexander submits an unexpected, frank opinion regarding the effect of analytic therapy. (The substance of the dialogs was indorsed by each member who took part in the discussion.) Alexander says, on page 90: "I doubt if anyone should risk the terrific disturbances that go with any thorough analysis unless he is in a serious emotional jam." That is the opinion of analytic therapy held by one of its main proponents. I did not intend to take up the subject of analytic therapy, but I think it is interesting to get some of these sidelights. My opinion as to the devastating effects of therapy I have expressed elsewhere.

The thing which interested me particularly with regard to the paper on tumors of the brain with psychoses was that in former days one was rather inclined to associate mental disturbances with frontal tumors. In the list of tumors given by Drs. Henry and Jamieson it was noteworthy that there were relatively few frontal, but more parietal and temporal, growths. It was brought out that many of the psychoses associated with tumors of the brain are coincidental.

Dr. Wechsler's thoughtful paper is naturally one that I am glad to indorse. He has expressed my feelings on the subject. I wish to commend him, as a fellow neurologist or a fellow neuropsychiatrist, for the way in which he presented the subject. One thing that I liked especially was that he said that psychoanalysis is one of many methods. That point is generally overlooked. Neurologists who are willing to acquire as much knowledge as possible from any source are glad to acknowledge the many excellencies that they owe to psychoanalytic writers, but they do not forget that after all psychoanalysis is only *one* of the psychologic methods, and not necessarily *the* psychologic method. It is *a* psychologic method of approach, and perhaps an important one.

Dr. Glueck emphasized the difference between the conceptions of the neurologist and those of the psychiatrist. Although the former lays all possible stress on structure and function, disorders of function need not be dependent on changes in structure. One cannot, however, conceive of function without structure. Dr. Glueck is wrong in stating that the neurologist insists that "disorders of function of necessity involve modifications in structure." That is an absolutely unwarranted distinction between the "somatist or organicist" and the "functionalist or vitalist." The neurologist certainly does not believe that a difference in function always means a difference in structure. What he does maintain is this: One cannot imagine a function of the liver without a liver; one cannot imagine a function of the brain without a brain; one cannot imagine vision without the eye. One must have structure as the basis of function; but that a difference in function always implies a difference in structure no one will claim, particularly as it is known that the change may be a biochemical one. The neurologist does not insist that every change in function necessarily means a change in structure; at least it is not one that can be recognized by any of the means at the disposal of physicians.

Dr. Glueck, like many of his colleagues, is much intrigued by the "dynamics" of psychopathology. The word "dynamics" and a number of other words are so dear to the heart of every psychoanalyst that he cannot get away from them; but no one ever claimed that man was nothing but a machine, "a biologic mechanical contrivance for the transformation of energy which expressed itself in human life and human conduct." Long before the freudian doctrines were thought of, psychiatrists were wide awake. They tried to interpret mental conditions; they did not always fall back on sexuality, but there was very careful mental analysis. There was careful psychologic analysis, though no use was made of the term "mental catharsis." Physicians were not accustomed to think of the bowels when they thought of the brain.

Dr. Glueck also speaks of the "joker in this scientific game, namely, that the refusal to accord psychologic data scientific validity was not science at all, but the crassest kind of prejudice, an inheritance of nineteenth century materialism." The truth is that there is no joker in the game at all, but what is claimed to be a joker is the opposition which some physicians offer. The latter think that there is no logical evidence for nine tenths of the facts put forward. I am encouraged a little by the fact that I had occasion to argue some of these points with a distinguished colleague, a psychoanalyst, who, when I said to him, "The trouble is with your interpretation and your facts; you have not proved your facts," replied that he was not at all concerned with facts and that he regarded psychoanalysis only as a convenient method of approach. If one is not going to talk of facts, the discussion will be brief, as in all scientific investigation one is accustomed to base theory on facts. If the psychoanalyst is not going to consider facts, or does not care whether his facts are correct, he will have to be classed in an entirely different group of scientists.

Dr. Glueck also said: "All of this must remain unintelligible if one limits his vision to a psychology of consciousness or the conscious self and refuses to accord equal consideration to the vastly more important psychology of the unconscious." I should not accept that statement for a moment, nor would any psychiatrist accept the statement that the unconscious is vastly more important than the conscious. A distinguished colleague of mine said that he was not going to

"sell out" to the unconscious. Freud has given a tremendous number of interesting observations regarding the unconscious; one enjoys them, but neither he nor any disciple has proved that conduct, overt behavior, is controlled by the unconscious. It may be modified by it, but it is not controlled. No lawyer or judge would agree with the doctrine that criminal actions are the result of unconscious motivation. They may sometimes be influenced to some extent by unconscious motivation, but one must maintain that people are all responsible for their actions. They must be consciously responsible and cannot hide behind a theory of unconscious motivation.

Dr. Glueck said that "psychoanalysis is to traditional psychiatry what histology is to anatomy." Yes, histology enlarged the knowledge of anatomy, but every observation in histology had to be corroborated before it was accepted. The psychoanalyst asks one to accept statements on his mere say so. Submit the claims to the neuropsychiatrist. What is true and good in the doctrine will stand the test of discussion; what is false or unwarranted will go to the wall. Dr. Glueck said: "The concept of the unconscious and of infantile sexuality as well as the so-called libido theory are no longer controversial topics." I must heartily disagree with him; they are still controversial topics, and I believe that if the members of the society will accept my suggestion and arrange at some future date for a detailed discussion of these various topics they will find that libido and infantile sexuality along freudian lines, the Oedipus complex and the unconscious are topics that are open to honest discussion and to honest differences of opinion.

DR. SMITH ELY JELLIFFE: Dr. Kubie's paper interests me greatly, chiefly from the standpoint of comparison of the inner meaning of children's utterances as studied today and as noted when I was intent on studying my five children, in the beginning of this century, from the point of view of the classic writers, Preyer and Sully, and others of that time. All I can say is this: I looked through the wrong end of a telescope at what was going on then, and I think that now one can look through the right end of a microscope.

While I was reading and listening to the presentation of Drs. Jamieson and Henry, so many interesting and suggestive thoughts arose that one might discuss them indefinitely. I agree with the general thesis that the presence of a tumor of the brain practically always gives rise to modifications in behavior. They may be slight, but careful psychiatric examination will nearly always bring them out. Even the dream technic has enabled me to suspect the presence of a tumor of the brain in two cases in which it was not evident on careful neurologic examination; in one case it was four years, and in the other, six years, before the tumor was sufficiently developed for surgical intervention to be considered.

I am in complete agreement with the speakers when they state that there is no characteristic psychotic picture in cases of tumor of the brain. All I should do if I discussed the situation further would be to elaborate what has been said. There are psychotic patients in whom tumors develop concomitantly with the psychosis; this development modifies the psychotic picture greatly. There are various irregular psychotic pictures caused by a tumor of the brain alone.

One note of minor dissent may be made regarding the rarity of euphoria. A striking experience make me mention this. I once saw a man, aged about 35, in a European hospital, who was regarded as hypomanic by a professor of psychiatry. For some reason I had a "hunch," based on the euphoria, which showed some features of classic *Witzelsucht*, that he had a tumor of the frontal lobe. All the neurologic signs were negative. He had been minutely examined; nevertheless, I persuaded an assistant to repeat the olfactory tests. They gave apparently negative results, but I persisted and claimed that the tests were not adequate. They were too artificial. My assistant and I tried first the smell of the patient's own undershirt and then that of his next door neighbor. We found a definite olfactory variation. He died that night, and a large frontal gumma was found at autopsy. Later, I saw a woman, of about the same age, who also had "hypomania," with much the same type of *Witzelsucht*. When asked how much was seven times eight, she laughed and said: "That's a cinch; that's my

milk bill." She cracked jokes all day long while in euphoria. In this case a large frontal tumor was found.

Changing the order of the discussion slightly, I wish to express my appreciation of Dr. Glueck's remarks. In his recital I find a statement of the issues involved as clear and as limpid as that of Dr. Wechsler is turgid and troubled.

Hence I pass to Dr. Wechsler's paper. I am a bit disappointed that one who is usually so clear and alert a dialectician was so confused in his presentation as to verify his own closing dissatisfaction, not so much on the basis of briefness of presentation, as by a grand pot-pourri of assumptions.

I would cross arms, though not too savagely, with him on his paradoxic opening statement. Dr. Wechsler is too able an epistolologist not to know that all "facts" are but the outcome of hypotheses and theories, and that hence the statement of conflict between "theory and fact" is spurious. I am, moreover, persuaded that there is a great deal of idealistic discussion of "scientific experimental evidence," not only in neurology but in psychology.

I missed altogether any precise definition of what Dr. Wechsler might mean by "neurology" or the "neurologic point of view." For myself, I feel that he creates pseudoproblems, and not very clearcut ones. It may be recalled that in the textbook that Dr. Glueck has generously referred to (Jelliffe and White: Diseases of the Nervous System: A Textbook of Neurology and Psychiatry, Philadelphia, Lea & Febiger, 1915), Dr. White and I spoke of vegetative neurology, sensorimotor neurology and symbolic neurology. In the introduction to the first edition (1915) we wrote:

"Man is not only a metabolic apparatus, accurately adjusted to a marvelous efficiency through the intricacies of the vegetative neurological mechanisms, nor do his sensori-motor functions make him solely a feeling, moving animal, seeking pleasure and avoiding pain, conquering time and space by the enhancement of his sensory possibilities and the magnification of his motor powers; nor yet is he exclusively a psychical machine, which by means of a masterly symbolic handling of the vast horde of realities about him has given him almost unlimited powers. He is all three, and a neurology of today that fails to interpret nervous disturbances in terms of all three of these levels, takes too narrow a view of the function of that master spirit in evolution, the nervous system."

From this broad point of view, I think that the antitheses which Dr. Wechsler brings up are as false and futile as he himself states the dualisms of "somaticist" and "functionalist" to be. Just as every Casey knows that one needs a bat to hit a ball, so every physician knows that structure and function are one; that a purpose, a drive, a wish, continued long enough, will develop a structure to facilitate the main issues of the purpose. No scrutiny on earth can tell, from the bat or from the ball, whether it is going to be a foul ball or a two bagger, go into the bleachers or be a strike-out; and in the same way no amount of scrutiny of physical, chemical or biologic picture or anything that is structuralized is going to reveal the full extent of the functioning behavior, in spite of all the "scientific experimental evidence" adducible.

If by "neurology" Dr. Wechsler means what I think he avoids saying, that it is the function of partial structures of the nervous system, then I feel that such a neurology is as incapable of solving the problems of psychiatry as is arithmetic, a limited series of mathematical assumptions, of solving the problems of einsteinian relativity. For myself I see no need of or sense in limiting the meaning of the term neurology to such comparatively simple integers.

I also take issue with Dr. Wechsler on his slur on "anthropomorphism." Everything that man does has to be anthropomorphic. He *is* "Anthropos" and even his gods—neurologic as well as psychiatric—are made in his image. The issue here, like that of "theory," is whether the anthropomorphism is good or false. To call a thing "anthropomorphic" means nothing. In what sense is the anthropomorphic conception of heredity any more serviceable than that of the chromomere, save that one is a static concept that cannot be used, while the other is of dynamic and pragmatic value. The glibbest of all stereotyped phraseologies are those of

"logic." I find myself in sympathy with a recent writer on the philosophy of the sciences who would claim that logic and mathematics are not knowledge at all. They are only a set of rules to guide one in the game of thinking; they have no application outside of the game. The kantian categories have been nothing but habits of thinking proved useful ad hoc. That is, one proves only what one has already assumed, as in mathematics. All men are mortal. Aristotle is a man; ergo Aristotle is mortal. The whole statement has been made in the first sentence, and as no one knows all men, it may be hocus pocus at that.

I am in total disagreement with Dr. Wechsler that statistical agreements will be of service in advancing the value of psychoanalysis. Statistics do not belong to an inductive methodology, and no inductive methodology has any interest in philosophy per se, which is largely a deductive methodology, useful in its sphere.

My chief comment is that Dr. Wechsler maintains that a good neurologist should be a good psychiatrist, and that a good psychiatrist should be a good neurologist; and the tendency of his argument with which I can agree is that one can be a good neurologist with a comparatively limited knowledge of anatomic and physiologic data about isolated aspects of the functioning of the body, but to be a good psychiatrist one has to know as much as God. This is tantamount to saying that there can be many good neurologists, but few good psychiatrists. If there is any use in stating an antithetic problem, one must limit the neurologic point of view to the limited aspects of partial functioning, whereas psychiatry becomes a "whale of a job."

In this connection, I can repeat a remark of Professor Perry of Harvard, who in a charming essay on the "Uses of Philosophy" defined the specialist as one who learns more and more about less and less until he gets to know everything about nothing, whereas the philosopher is one who learns less and less about more and more until he gets to know nothing about everything. The neurologist and the psychiatrist thus meet on a common ground, and with the psalmist one may agree that all is vanity, this matching and comparing. So let them both go about their business as doctors as they always have done and worry through, doing the best they can, each with his vanities, his prejudices and his illusions.

"The vision of the world as an embodiment of reason through and through is thus an idle dream, not only because the flux of sensation from which we start can never be distilled away into concepts, but also because knowledge is a projected shadow of ourselves and a pragmatically verified interpretation is the nearest approach" to the world outside.

DR. ISRAEL STRAUSS: I think that the authors of the paper on "Mental Aspects of Tumors of the Brain in Psychotic Patients" are right when they say that they cannot classify the mental symptoms in tumors of the brain as being diagnostic of tumor, except that, as Dr. Jelliffe pointed out, in some cases of tumors of the frontal lobe one finds a state of euphoria, a state of exaggeration and frequently a decided defect in memory. The same thing can to a certain extent occur in tumors of the temporal lobe. To Dr. Sachs it was a surprise to find mental symptoms in cerebellar tumors, and as I looked over the records submitted I did not find true mental symptoms in the three cases of cerebellar tumors. It has been a rule for neurologists, and for psychiatrists, to regard psychotic symptoms as supratentorial. I have never seen a case of infratentorial neoplasm that showed psychotic manifestations except when the patient had had the tumor for a great many years.

I have been wondering whether I am a neurologist or a psychiatrist. I practice medicine in both fields. I really think that every neurologist practices psychiatry. I am certain that if he did not he would starve. Moreover, I am sure that those who call themselves psychiatrists realize that there is a brain, that the brain functions, and that if one removes it, so far as I know, the wish of fulfilment does not seem to manifest itself. What is the use of talking about structure and function, when one knows that function cannot occur unless structure is present? The neurologist may hope that some day he will be able to demonstrate something material with which he can correlate specific function. I saw a woman

last summer who had a functional disease (a term that I hate, because every time I use the word "functional" I feel that I am ignorant in the philosophic sense). I sent her to a psychiatrist for analysis. She was examined by a hematologist and a gastro-enterologist; roentgenograms of the gastro-intestinal tract were made, and everything was done that can be done in modern medicine. Yet I could see no reason for the patient's signs; she was sick and lost ground, finally began to vomit, and kept on vomiting. I fed her by tube; the only food that she would take was root beer. She died, and an examination of every organ in the body failed to reveal any structural abnormality. That does not mean that there may not have been some change in structure, but with the methods available one could not demonstrate a change. Even though I do not know what it is, I believe that function has some relation to structure.

I am closely wedded to the psychoanalytic school. I can see that a great deal has been explained by Freud, and I know that the psychoanalytic approach in the treatment of mental disease has made psychiatry popular. A few physicians in state hospitals are doing something with this method. They may be wrong in their interpretations; I do not care. I have seen many physicians who have made hypotheses that were wrong, but they had a basis on which to work.

Going back to Dr. Kubie's illustration about the chocolate, I want to show some little differences in mental attitude. Dr. Kubie told of a child, aged 3, who put his finger in the rectum and smelled the finger. Dr. Kubie jumped to the conclusion that the child noted that the odor was chocolate, because it noticed that its feces were of chocolate color and the consistency of chocolate. The difficulty with this example is the elucidation. Dr. Kubie would undoubtedly show the links which seem wanting in this connection. In order words, it seems to me illogical, or unscientific, to postulate a cause and effect relationship, for the reason that every step in this type of psychologic analysis is not portrayed; if one does not get every step in the mental process of the person who had the experience, the conclusion seems like a stretch of the imagination. Unquestionably, some of the interpretations that analysts make are of this nature, but who knows what they will be in the future? As Dr. Jelliffe says, the question is pragmatic. The psychoanalysts are working with something; they are trying to develop something. Neurologists cannot find fault with that. Their method is the same.

Dr. J. Ramsay Hunt: The question of the relation of the psychiatrist and of the neurologist to mental disorders is of interest, and I think that the papers of Dr. Wechsler and Dr. Glueck were excellent presentations from their respective points of view. I am more interested in the question of the union of neurology and psychiatry in terms of neuropsychiatry. It is my conviction that in the coming years there will be fewer differences between the two groups than at present, and that in the future the greater number of workers in this field will be neuropsychiatrists rather than neurologists or psychiatrists in the narrower conception of these terms. A neurologist, in this narrower sense, is a specialist with a smattering of knowledge of the neuroses and psychoses, while a psychiatrist is one whose chief interest has been the investigation and study of the major psychoses in institutions for mental disorders. The neuropsychiatrist, on the other hand, will I believe embody what was best in the old neurologist of broad outlook and training, in addition to the modern refinements of psychiatric diagnosis and psychotherapy. That neurologists have always played a conspicuous rôle in the development of psychologic medicine is shown in the history of the modern movements in psychology, for do not forget that Charcot was a neurologist and Freud a neurologist. This neurologic interest and point of view will, I believe, be continued in neuropsychiatry. If one studies the origin of neurology and what is now termed psychiatry as special fields of medicine, one finds that neurologists as specialists in disorders of the nervous system came from general hospitals, their interests closely related to those of internal medicine, neurophysiology, neuro-anatomy and neuropathology, but also to psychiatry as it existed in general hospitals and in private practice in that day. This training produced a well rounded specialist, who may be termed a neuropsychiatrist.

The psychiatrist, on the other hand, came from state and private institutions for the care and treatment of patients with mental disorders, where he was also physician and neurologist, but above all a psychiatrist concerned largely with the study of the major psychoses. He, too, was interested and made many important contributions in the field of neuro-anatomy and neuropathology; such a point of view found its greatest expression in Kraepelin's important textbook (Psychiatrie. Ein Lehrbuch für Studierende und Aerzte, ed. 4, Leipzig, Johann Ambrosius Barth, 1921).

At the present time, great changes are taking place, due largely to important developments within the fields of both neurology and psychiatry. One of the outstanding developments is the interest in problems of the mind. In the medical group, both neurologists and psychiatrists have participated in these activities. In speaking of the rôle played by neurologists in advancing the problem of mind in its relation to medicine, one need only mention such names as Hughlings Jackson in England, Charcot and his pupil Janet in France, Freud in Austria and Morton Prince in this country.

It is true that a neurologist is interested in the function of all levels of the nervous system, but through the work of masters like Charcot and Freud, one sees what important psychologic implications such studies may have when they are carried into the cerebral cortex and enter the realm of mind. Therefore, in any future realinement of this great field of the nervous system, it is certain that the neurologic point of view will not be confined to the mere study of fragments and parts of the nervous system, as some psychiatrists would have one believe, nor, on the other hand, will the psychiatric point of view be limited to the study of what might be termed "universals," under the guise of the total personality; the men who will represent the whole field will be trained in both disciplines; in other words, they will be neuropsychiatrists.

Some of these physicians will always lean more toward internal medicine and organic neurology, while others, as in the psychiatry of the past, will be concerned chiefly with institutional psychiatry, but the greater number will be neuro-psychiatrists, and will combine all that was best in the old neurology and the new psychiatry.

Dr. Foster Kennedy: Surely in all of this matter there have been too many words. Everybody tries to explain the unknown by something equally unknown. It is like looking in the dictionary to find the word "zest" meaning "vitality," and then looking up "vitality" to find it means "zest," and unless one knows beforehand what zest and vitality mean one is no wiser. Every fact, every circumstance in the world can be looked at in two different ways—perhaps three or even four. The first chapter of Genesis is true, and so is Clodd's Story of Creation. If one is educated and wise, he will know that both are true. It is foolish for an atheist to say, "There is no God," and wait for the lightning to strike him. The atheist is too trivial for God to pay any attention to. It seems equally foolish and contrary to experience to say that God takes care of people as "Personal Providence," guarding the very hairs of their heads. In the contemplation of the unknown, one believes emotionally and in extremes. You heard Dr. Jelliffe exaggerate, trumpeting like Boanerges on the left wing, and perhaps Dr. Sachs like the ancient gods too far on the right. Physicians must believe that one cannot have intellect, dreams or ecstasies, unless one has a fine inherited neuronic endowment. The *strategic* outline and limits of mind are laid down by inheritance; the *tactical* details of mind are worked in by stimulation, by the social attributes of education and by the molding pressures of sex, the herd and hunger. Freud has done a great service in demonstrating the phylogenesis of mind and of behavior; he has shown that minds and methods of thought and feeling, as they develop, go through the same stages as those through which the race has passed—just as bodies have gone through such stages. This portrayal of the phylogenesis of mental mechanism, I believe, will live; much else of freudian dogma, posterity, I believe, will discard. As a therapeutic instrument, psychoanalysis is often of service. But it does not displace medicine, and it does not, as

Dr. Wechsler wisely says, comprise a philosophy of medicine or a philosophy of life. It is the phylogenesis of personality and has offset and compensated for the materialism of the nineteenth century. Psychoanalysis is valuable until physiology and other sciences assume a larger stature, and it will give out of its present material a precious contribution to the study of the workings of the mind. It would be well to stop thinking about the *neurologist's* attitude to mind, and the *psychiatrist's* attitude to mind, and perhaps the gastro-enterologist's attitude to mind. All of them are physicians, and as such they must study man, in his material structure and in his emotional and mental functions; and if he has a soul, let them pray for it!

Dr. Louis Casamajor: In the paper of Drs. Henry and Jamieson I was interested in the fact that in many of these cases the psychosis appeared before the tumor was discovered. That of course does not mean that the psychosis really preceded the tumor, for one cannot say just when a tumor begins. I do not think that one is justified in drawing the conclusion that the tumor and the psychosis may bear no relationship to each other. With Dr. Jelliffe, I believe that all cases of tumor of the brain show some psychosis which careful examination will reveal.

With regard to the last two papers I feel that there has been a bit of fraud about this whole discussion. I expected that there would be a controversy, but apparently everybody agrees on the subject. Each one who has participated in the discussion seems to disagree with what he thought some one else was going to say, but so far as the general tenor of the whole discussion goes, apparently all the speakers are talking about the same things in the same way. Obviously, Dr. Wechsler was scolding somebody, but I could not find out just who it was that he was scolding. I have an idea that at the bottom he was scolding himself. I doubt if there is much difference between neurology and psychiatry. The exponents of each have somewhat different points of view, depending on their training, but they all mean about the same thing. As a general rule, the psychiatrist knows little of neuro-anatomy and neuropathology, and he tries to pretend that these two subjects are of no importance rather than take the time to learn about them. The neurologist, on the other hand, too frequently knows little about the cultural side of the problem and little of the social side, and as he does not want to know anything about them he says that they are of no importance. As I listened to the papers, it struck me that this was something like an argument being carried on between men who spoke two different languages, trying to talk about the same thing. I was interested and pleased, however, to note that the common ground on which neurologists and psychiatrists met was psychoanalysis. If there is anything which will bring the two together and make a true specialty of the study of the nervous system, it will probably be psychoanalysis, because in psychoanalysis one finds a language which both sides understand clearly. Probably these discussions are of value, for out of them may come a solution to the entire problem. Before that solution is reached, however, I think that both neurologists and psychiatrists must know a little more about what they are doing and be a little more humble in the approach to the question. Let them take into consideration the other person's point of view and try to find out what he means, and perhaps some day they may find that there has never been any controversy.

NEW YORK NEUROLOGICAL SOCIETY

Regular Meeting, Dec. 6, 1932

Henry Alsop Riley, M.D., *President, in the Chair*

Spinal Epidural Abscess. Dr. S. P. Goodhart and Dr. Nathan Savitsky.

A woman, aged 22, who had been married one month, was admitted to the Morrisania Hospital on March 14, 1932, with severe pains in the back which she

had had for two days. A furuncle on the chin had been incised two weeks before admission. She walked into the hospital; her temperature was 101 F.; severe tenderness and hyperalgesia were noted in the lumbosacral segments. On the next day she experienced difficulty in voiding urine; some rigidity of the neck was evident. All reflexes were active; there was no Babinski sign. Two days after admission, flaccid paraplegia with urinary retention became complete within twelve hours. Lumbar puncture showed complete block, with a Froin syndrome; there were 14 lymphocytes in the spinal fluid. There was loss of all types of sensation below the eleventh dorsal vertebra, with diminished sensation to the fourth dorsal vertebra. A diagnosis of epidural abscess metastatic from the furuncle on the chin was made. At an operation on the same day, the lamina of the sixth dorsal vertebra was removed; pus drained from the epidural space, from which Staphylococcus aureus was cultivated.

The patient improved slowly but definitely after the operation, especially after the injection of about 20 cc. of air under low pressure on June 13, after a partial block had been found and studies with iodized poppy seed oil 40 per cent had revealed probable subarachnoid adhesions. She now has an atypical Brown-Séquard syndrome, but is able to get about with braces. The sphincteric function is much improved.

In 53 cases reviewed in an incomplete survey of the literature, 8 patients recovered after operation, usually incompletely. Early diagnosis is important, because severe damage to the cord usually sets in early. This is due largely to functional circulatory changes within the cord, as was recently suggested by Pollak.

ALEXIA FOLLOWING INJURY OF THE HEAD. DR. S. P. GOODHART and DR. NATHAN SAVITSKY.

A German sea fireman, aged 45, was struck by an automobile on March 9, 1931, and rendered unconscious for two days. He could neither read nor recognize letters after this accident. He complained of headaches and dizziness, which were relieved a number of times by lumbar tap. He had also had convulsive seizures and other less clearly defined attacks of loss of consciousness. While he was under observation at the Morrisania Hospital in April and May, 1932, neurologic examination revealed pure alexia without other focal signs. A right hemisensory defect was noted, which was not organic in pattern. On the face and upper limbs were scars from a burn sustained in the explosion of an oil tank in 1905. There was no agraphia. The patient could not read his own handwriting. There was no other evidence of optic agnosia. Body orientation was intact. The blood pressure was 150 systolic and 106 diastolic, and the heart was enlarged to the left. An encephalogram showed a collection of air over the left parietal region. The readings of the spinal fluid pressure were within normal limits.

Later, the special senses on the right side were found to be involved. Early in October, 1932, a favorable financial settlement of the case was made. Examination on Dec. 6, 1932, showed that the alexia persisted, with improvement only in the recognition of a few letters. The patient could not read words. The sensory changes on the right side of the body were less marked. The deafness in the right ear was entirely gone.

We think that the alexia was due to a lesion somewhere between the angular gyrus and the left occipital cortex.

Massary recently contributed an excellent review of this subject. Alexia following injury to the head is rare. Alexia of organic origin as the sole focal sign is indeed unusual. Right hemianopia or its residua are practically the rule, though Lannois and Tournier and Shuster reported cases unaccompanied by changes in the visual field. However, even these authors report hemiparesis and aphasia.

The associated sensory changes in our case suggest the possibility that the alexia is hysterical. The clinical picture, however, certainly resembles closely that of the so-called pure alexia of Dejerine—intact writing and the preservation of the reading of numbers. We think that this dissociation favors the organic nature

of the alexia. If it were functional or simulated one would certainly expect a more global defect. The alleged occurrence of epileptiform attacks favors the presence of organic brain disease. If this syndrome is psychogenic, it is, to say the least, unusual. The defect has now persisted for twenty months, in spite of the fact that the undoubted functional changes are disappearing.

SUBARACHNOID HEMORRHAGE DURING AN ASTHMATIC ATTACK. DR. S. P. GOODHART and DR. NATHAN SAVITSKY.

A man, aged 34, was admitted to the Morrisania Hospital on April 3, 1931, with a history of recurring attacks of asthma for two months. Physical examination on admission gave negative results except for diminished breath sounds and musical râles all over the chest. Three days after admission, the patient complained of severe headaches after an asthmatic attack. On April 13, there was a series of severe attacks, which were not relieved by injections of epinephrine hydrochloride. The attacks continued. On April 15, intense headache followed a few minutes after an injection of 10 minims (0.6 cc.) of epinephrine. Examination on that day showed a meningeal syndrome, drowsiness, mild bilateral cerebellar signs, with lateral coarse nystagmus, and clonic movements in the right upper limb. Lumbar and cisternal tap revealed uniformly bloody fluid, which did not coagulate. The temperature remained at 103 F. for two days; then progressive improvement set in. On May 3, 1931, there were no signs of meningeal irritation. Berri reported a similar case in 1930.

SUBARACHNOID HEMORRHAGE FOLLOWING CISTERNAL PUNCTURE. DR. S. P. GOODHART and DR. NATHAN SAVITSKY.

A man, aged 24, had a chancre of the lip in June, 1929. The Wassermann test was positive at the time. During a few months he received eighteen injections of silver arsphenamine and five doses of mercury intramuscularly. On Feb. 2, 1932, 0.2 Gm. of silver arsphenamine was given. On February 3, a cisternal tap was done in the outpatient department of a New York hospital; the patient said, "After they put the needle in, I felt a shock on the right side of my body like 10,000 volts. The shock passed, and my legs and arms were numb. I was dizzy and waited half an hour in the clinic. I then went home with a headache. I spent a terrible night with no sleep. The next morning I couldn't move my head."

He was admitted to the Morrisania Hospital on Feb. 5, 1932, with signs of meningeal irritation—stiff neck and bilateral Kernig sign. The spinal fluid was uniformly bloody and did not coagulate. The Wassermann reactions of the blood and spinal fluid were negative. The patient complained of severe pain in the upper part of the right side of the face. There was diminution of pain and temperature sensibilities in the distribution of the first division of the right trigeminal nerve. Touch was spared. There were also painful dysesthesias on stimulating this area.

Improvement was rapid and progressive. On Feb. 19, 1932, there was no sign of meningeal irritation, but the sensory changes in the distribution of the right fifth nerve persisted. They were still present on May 19, 1932, though less marked.

Nonne and Bennholdt-Thomsen reported fatal cases of subarachnoid bleeding following cisternal puncture. Eskuchen and Molhant described cases with recovery. Nonne's case was due to the rupture of an anomalous arteriosclerotic vessel. Atrachian and Dielman discussed the probability of puncture of the medulla during the tap, with recovery. We believe that the medulla was punctured in our case, as there was evidence of injury to the descending root of the fifth nerve. The needle used in the puncture in this case was too long and was not provided with a guard.

DISCUSSION ON PAPERS OF DR. S. P. GOODHART AND DR. NATHAN SAVITSKY

DR. J. H. LEINER: Were the misspellings in writing in case 2 due to poor education or to agraphia?

DR. NATHAN SAVITSKY: The man had an elementary school education. He is fairly intelligent, but not well schooled. He has been a seaman all his life.

DR. PAUL SCHILDER: Does this man always write in comparatively small letters? I think that there are certainly some difficulties in writing large letters, and I have an impression that there is a micrographia. It is possible that the psychogenic sensory disturbances are superimposed on organic ones due to lesion of the parietal lobe; at least, it is difficult to exclude that. I am of the opinion that there is one group of cases of injury to the parietal lobe in which the patients react in a peculiar way to bodily disturbances. I am observing a patient in Bellevue Hospital with a lesion of the parietal lobe, which was also due to an injury of the head. He has hypochondriac complaints about his right side, on which a parietal disturbance of sensibility is present. I mention, therefore, the possibility that the functional disturbances may cover some organic disturbances of sensibility. I think that there can be no doubt that this is a case of alexia. But the patient shows at least a minor degree of agraphic disturbance. It seems to me also that there is a slight agnosia of the finger. Whenever examinations are made carefully, one generally finds in such cases that if one function is very much disturbed, psychologically allied functions show some minor impairment. These appear when the patient is generally fatigued. The case leads, therefore, to problems of interest in the realms of aphasia and agnosia.

DR. S. P. GOODHART: The sensory features in this case seem to us to be purely psychogenic. An underlying organic defect might, in a sense, be assumed in almost every case. This brings one to the boundary of the disputed problem of the relationship between the organic and the psychogenic.

DR. PAUL SCHILDER: It is difficult to say whether or not a psychogenic disturbance is superimposed on an organic basis. I do not doubt that there is a psychogenic disturbance of sensibility, but I cannot exclude the possibility that there is an underlying organic disturbance.

DR. J. H. LEINER: Did this man really forget to speak English or to read English? Could he write English before?

DR. NATHAN SAVITSKY: No.

DR. J. H. LEINER: During the war, I saw, with Dr. Climenko, a patient who, following a nasal submucous operation, experienced an infection which was followed by an abscess of the brain, localized in the region of Broca's area; there were right hemiplegia and motor aphasia. Following the operation the patient spoke only Polish. A number of months later, he could speak English. The memory pictures of his mother tongue were capable of recall first; the acquired tongue returned later. May I ask how long it is since this man's accident?

DR. S. P. GOODHART: Twenty months.

DR. J. H. LEINER: This case may prove to be purely organic.

DR. IRVING J. SANDS: Cisternal punctures are not infrequently followed by bleeding. If such cases were reported as frequently as they occur, it would be realized that hemorrhage complicates cisternal puncture in many instances. In my pathologic collection I have two cases. About two years ago I reported a case of subarachnoid hemorrhage complicating encephalography and terminating fatally (ARCH. NEUROL. & PSYCHIAT. **24**:419 [July] 1930).

The question of the sensory disturbances and their relation to a possible puncture of the medulla is one that is not so readily answered. I think that sensory disturbances such as those described may be accounted for by the blood coming in contact with the roots of the trigeminal nerve. I have reported such a case (ARCH. NEUROL. & PSYCHIAT. **21**:37 [Jan.] 1929). A medullary injury that would produce subarachnoid bleeding would be much more dangerous and would probably end fatally.

Asthma is relatively common and is rarely complicated by cerebral hemorrhage, especially in young people. Pertussis may be complicated by hemorrhage. It is possible that in case 3 the subarachnoid hemorrhage may have been caused by

venous stasis resulting from the asthmatic attacks. May not the subarachnoid hemorrhage and the asthma occur as independent conditions, not related to each other?

In the second case there are important sociologic and medicolegal implications. I have no patience with the idea that there is a psychogenic element in the symptom complex. A man who has received an injury to the head and has been rendered unconscious for several days has sustained an injury to the brain and is entitled to have so-called psychogenic signs. There are no available tests that will tell precisely what has happened to this man's brain. Frequently, so-called experts after a hurried examination, years after an injury to the head, testify in court that the patient is suffering from "nervousness" or is even malingering. Not long ago, a man sustained an injury to the head and was unconscious for several days; subsequently he sued for damages. Several neurologists examined him and asserted that the symptoms were psychogenic. On examining him, finding no organic neurologic signs, I informed the lawyer that the man was hysterical. The man contracted pneumonia and died; at autopsy there were characteristic signs of injury to the inferior surfaces of the frontal lobes. That case taught me a great lesson. To say that a man's symptoms are psychogenic when he has received an injury to the head followed by unconsciousness of several days' duration is adding insult to injury.

DR. S. P. GOODHART: Dr. Sands' remarks are pertinent. The medicolegal aspect of this case has been taken care of. Sensory examination suggested psychogenic features—its marked limitation, involvement of the special senses on the same side, gradual improvement and appreciation of sensory stimulation. The alexia is organic. I think that Dr. Sands must have the thought that Dr. Schilder has expressed — that one must be careful in considering these cases entirely psychogenic.

DR. NATHAN SAVITSKY: In reference to the fourth case, it was stated that the sensory symptoms were due probably to blood trickling on the trigeminal sensory root. That is unlikely. It is rarely, if ever, encountered in the usual case of subarachnoid hemorrhage. The symptom is due probably to puncture of the medulla and injury of the descending root of the fifth nerve. There was diminution of pain and temperature sensation with dysesthesias. Touch was apparently preserved; there were hypalgesia of thalamic type and, in addition, following the injury, signs suggestive of injury of the spinothalamic tract.

DWARFISM AND OCULAR DEFECTS IN HEREDOFAMILIAL DISEASE OF THE CENTRAL NERVOUS SYSTEM. DR. BÉLA MITTELMANN.

Interest in these cases is twofold: 1. They present an unclassified type of heredofamilial disease of the central nervous system. 2. They show other singular somatic signs associated with the neurologic manifestations. This study is based on the examination of the accessible members of a Greek-Jewish family. In three generations four members of the family were found to present neurologic signs; one was manifestly ill; another showed other obvious somatic, but latent neurologic signs, and the third and fourth manifested chiefly neurologic signs.

Two sisters, one aged 16 and the other 6 years, presented signs of a pathologic condition of the pyramidal and cerebellar tracts—ataxic gait, tremor of the head, undulatory nystagmus in all positions of both eyes, marked intention tremor of both upper extremities in the finger-to-nose test, increased reflexes, changes in the abdominal reflexes and Babinski's sign. Both were markedly stunted in growth, but proportionately built. The x-ray pictures showed normal ossification of the bones. Both had a suggestion of saddle-back nose and marked hirsuties. The basal metabolic rate was normal. Both showed marked hyperopic refractive errors of both eyes.

An uncle of the two sisters had exaggeration of all deep reflexes, changes in the abdominal reflexes, left facial weakness of the upper motor neuron type, bilateral weakness of the sixth nerve, deficiency of convergence and hypermetropia of both eyes of 1 diopter.

An aunt had undulatory nystagmus of both eyes, congenital cataract of both eyes and myopia of 10 diopters.

These were the four members of the family who presented neurologic signs in three generations. The great grandmother of the first two patients mentioned was, according to uniform reports of the family, markedly stunted in growth, being no taller than the dwarf, aged 16. Most members of the family in the second and third generations conformed to the family type, with short stature, suggestion of saddle-back nose, some tendency to hirsuties, refractive errors of the eyes and low mentality. Some members of the third and fourth generations showed marked divergences of somatic traits, always resembling the extrafamilial parent. The parents of our first two patients were blood relatives, the mother having married her uncle. The symptoms in the two sisters are probably the result of an exaggeration of the recessive abiotrophic tendencies of the generations to which the other two patients belong.

The cases are unique in that they showed a combination of dwarfism with a heredofamilial disease of the multiple sclerosis type, but in other respects they have more general implications: (1) They show the existence of a heredofamilial disease which resembles multiple sclerosis without remissions; (2) in heredofamilial diseases of the central nervous system other systems are frequently involved.

DISCUSSION

DR. S. P. GOODHART: I had expected that Dr. Mittelmann would show more defects in the ocular mechanism. Speaking of the dystrophies, I thought that he might mention the myotonia atrophica related to the dystrophies. He spoke of the chemical findings described by Janney, Isaacson and me, referring to suggestive metabolic changes. The metabolic changes certainly warranted the conclusion that there was evidence of the influence of the endocrine glands in the progressive muscular dystrophies. As I recall them, the significant findings were: decrease in the preformed creatinine and abnormal presence of creatine in the urine; a low level of creatinine and a normal level of creatine in the blood, and hypoglycemia and delayed untilization of dextrose.

DR. WALTER TIMME: The question of growth is not only a question of the action of the hormonal secretion of the anterior lobe of the pituitary gland. That is possibly only one of the growth hormones. Other elements, such as a lack of calcium and phosphorus, plus a normally acting sympathetic nervous system, play a part. Just as there are in the circulatory system the vasa vasorum, so in the nervous structures there are the nervi nervorum, by which the nervous structures are controlled trophically. Growth and other metabolic processes, or glandular activities, are similarly controlled; when there are combined disturbances of these, I think that there is an abnormal vegetative nervous system which is affecting the sensory nervous system, as well as the glandular elements, to produce a combination of two syndromes seemingly as far apart as the poles and yet clearly connected in their trophic control.

DR. BÉLA MITTELMANN: I forgot to mention one ocular defect. There were blue spots on the sclera of the younger girl.

My remarks concerning the evaluation of the metabolic disturbances apply only to my own cases. As Dr. Goodhart stated, definite metabolic changes are present in muscular dystrophy, but the interpretation is difficult. It is doubtful whether the disturbance is in the anlage or in other organs regulating metabolism, that is, whether the disturbance of the endocrine glands is primary and the muscular disturbance is secondary. At present, one cannot decide.

The point which Dr. Timme mentioned is of interest. The cases of Pelizäus and Merzbacher showing severe involvement did not give evidence of stunting in growth. That does not exclude the possibility that in another group of cases the vegetative nerves regulating growth are affected. Furthermore, it is striking that in cases of Friedreich's ataxia with bony changes one practically never finds dwarfism. So, although Dr. Timme's interpretation is interesting there is no

evidence to prove it. Perhaps the best examples of such possibilities are cases in which infantilism or dwarfism develops after injury of the head during the period of growth. It seems that trauma more frequently affects the "centers of growth." I forgot to mention an example of the combination of dwarfism with familial disease described to me in a personal communication from Dr. Schilder. He observed a colored family the members of which uniformly presented extrapyramidal involvement, dwarfism and marked lordosis. His cases are another example of a peculiar syndrome running through members of one family, with involvement of other systems in addition to the central nervous organization.

ABNORMAL EXCRETION OF THEELIN AND PROLAN IN PATIENTS SUFFERING FROM MIGRAINE. A PRELIMINARY REPORT. DR. HENRY ALSOP RILEY, DR. RICHARD M. BRICKNER and DR. RAPHAEL KURZROK, with the technical assistance of MARGARET CREELMAN, IRENE KIRKMAN and STANLEY GOLDMAN.

Hormonal studies have been made daily over a prolonged period of the urine of thirteen patients—11 female and two male—suffering from migraine. The period of observation has in each instance included a typical attack. In the urine of the female patients, the studies have embraced the quantitative estimation of female sex hormone and the identification of prolan. In the urine of male patients only the identification of prolan was included. No distinction was made between prolan A and prolan B.

Results.—1. Theelin was occasionally present in the urine of all but one of the women of menstrual age, and in this one the menopause was imminent. In the urine of one woman who had passed a natural menopause theelin was absent, as was the case also in that of another woman in whom the menopause had been induced by operation. In all of the cases in which theelin was demonstrated in the urine, the hormone was absent from the urine sporadically; when present the amount of theelin rarely exceeded 5 rat units per liter. Only exceptionally did the quantity of hormone reach from 10 to 20 rat units, which is considered the normal amount for women within the menstrual age.

2. No demonstrable relationship was determined between variations in the excretion of theelin and the occurrence of headache.

3. In all cases prolan was excreted. In the urine of the two women past the menopause and of the one approaching it prolan was present almost daily in large quantities; in the remaining eleven cases the hormone was demonstrated in the urine intermittently and in varying amounts.

4. In all the patients, twenty-nine individual headaches occurred. Headaches that continued over consecutive days were considered, for purposes of tabulation, as constituting a single attack. In two patients the headaches were so continuous as to constitute a state of migraine. Not being separable into single headaches, this prolonged condition could not be included in the number given (29). Twenty of the twenty-nine headaches were preceded or accompanied by the appearance of prolan in the urine. The number of days by which the appearance of prolan antedated the headache was determined by counting from the first day of the appearance of the hormone to the beginning of the headache.

It should be noted that frequently, and particularly when prolan first appeared several days in advance of the headache, its excretion continued for a number of days, terminating just before or concomitantly with the appearance of the headache. In the urine of one patient, prolan appeared on each of three consecutive days antedating the headache and disappeared with the occurrence of the headache. In the urine of another patient on one occasion prolan was demonstrated four days before the headache, but continued to appear for three of the four days. In another instance, the appearance of prolan in the urine preceded the headache by an interval of six days, and the hormone continued to occur in the urine on each of the six days, failing to appear only on the day of the headache. In four instances the continuous excretion of prolan extended through at least a part of the period of the headache. In one case the prolan appeared in the urine for two days, was

absent for one day, and recurred coincidentally with the occurrence of the headache. The incidence of headache and the excretion of prolan limited to a single day coincided in only two instances. The interval by which the one antedated the other was in seven instances one day; in four, two days; in five, three days; in one, four days, and in one, six days. In the two patients presenting a state of migraine the excretion of prolan was practically uninterrupted. There was, therefore, a continuous relationship between the appearance of prolan in the urine and the occurrence of headache. In one patient, a practically continuous excretion of prolan occurred during the period of observation, but in this time only three headaches took place. In this patient it was therefore impossible to relate the headaches to any particular day when prolan was excreted.

5. In nine of the twenty-nine headaches no prolan-headache relationship was demonstrated. In seven of the nine headaches, however, the determination of an exact relationship between the appearance of prolan and the occurrence of headache was rendered impossible by the absence of specimens of urine. In the remaining two of the nine, the requisite number of specimens was obtained, but the headache occurred without the antecedent appearance of prolan.

6. Occasionally prolan appeared without the subsequent development of headache. Of the three patients showing almost daily excretion of prolan, one failed to have a headache on only one day; another was free from headache on only an occasional day, but the third, as stated, was free from headache during the major part of the time of observation. In only three of the remaining eight patients in whose urine prolan appeared intermittently did a headache fail to follow the excretion of the hormone.

7. Of the eight women of menstrual age, seven had attacks with menstruation. The relationship between menstruation, headache and the excretion of prolan could not be shown to differ from the headache-prolan relationship occurring at other times.

8. Nine female patients received injections of 2 cc. of the hormone occurring in the urine of pregnant women, and seven presented an attack of migraine within from four to twelve hours. The attack was either mild or severe but always presented the characteristics which were typical for the individual patient.

Only two men were studied during the period covered by this preliminary investigation. One man had six and the other nine headaches. In the patient with six attacks, the specimens of urine obtained preceding one headache were lost; all of the other attacks were associated with the excretion of prolan within a period not exceeding three days. In the other male patient, who had nine headaches, the specimens obtained preceding one attack were lost. Of the remaining eight attacks, only four were associated with the excretion of prolan.

The hormone occurring in the urine of pregnant woman was administered twice to the patient with six attacks, the injections being separated by an interval of six days, with the development of a mild headache three days after the first injection, but with no headache subsequent to the second injection.

DISCUSSION

DR. WALTER TIMME: It has been commonly believed that Aschheim and Zondek were responsible for the demonstration of the two prolans, A and B, in the anterior lobe of the pituitary gland. However, Wiesner and Crew demonstrated these hormones (which they called Rho I and Rho II) at least as early as Aschheim did; they also formulated the methods by which these hormonal substances can be separated from each other.

It is unfortunate that one cannot distinguish between prolans A and B at present, because each acts contrary to the other; there is doubt as to which of the two is meant. I think that an issue which might be clear is thereby confused. While one of the two prolans may produce headache, the other may alleviate it.

One of the criteria in this study was that the attacks of migraine should be associated with menstruation. As a fact, while most attacks of migraine are in

some way linked with the menstrual period, all are not. A further study must be undertaken with a view to determining the incidence, characteristics and causes of attacks of migraine occurring at times other than during menstruation. For instance, the menstrual attacks of migraine are said to diminish or cease altogether during the period of child-bearing. However, some patients have severe types of migraine at that time; it is only the menstrual type of migraine that ceases during the period of gravidity.

Dr. Brickner was careful to say that there is some connection between the prolan and the headache; I agree with him. I do not think that the connection is causal for the reason that investigators have considered that the attack of migraine is limited to the headache alone. The headache is only one part of an attack, which can be divided into three stages. The first stage lasts for from half a day to three days; during this stage there is no headache, and the patient has a feeling of well-being. Then follows the headache, which also lasts for an indefinite period—from half a day to three days. In the third or receding stage, there is relaxation of all functions, with a feeling of exhaustion that lasts a day or two. This would account for the fact that prolan appears in the urine a day or two before the headache begins. It appears with the initial enlargement of the anterior pituitary gland. No headache occurs as yet because the pressure has not increased within the sella. When the increase of pressure occurs, the headache begins. Prolan is not a product of the headache, but of the overactive anterior lobe of the pituitary gland. When studies are made, it will be found that a pituitary hormone is also released at the time of the headache. Before the headache the blood pressure is usually very low. A demand is made on the pituitary gland for an increased production of pituitary hormone; then comes the rise in pressure. At the beginning of the rise of pressure, before the headache starts, there is an increase of pituitary hormone in the blood; this increases for a time and then diminishes. Prolan will produce a headache on injection; pituitrin administered in a sufficient dose will cause a severe headache within from a half to one day, and so will some other products of the pituitary gland.

Other glands also are implicated. For instance, when insulin is given in too great a dose and therefore produces shock, the first stage of recovery is accompanied by severe migraine in patients who suffer from migraine. Certain hepatic disturbances are accompanied by severe migraine in those predisposed to these headaches. In attacks of migraine there is disturbance in the interchange of water. Just previous to an attack there is excreted only a small amount of urine, the cessation of the attack is ushered in by a large output of urine.

In migraine the pituitary gland is not necessarily diseased; it is endeavoring to perform a purposeful act, to overcome disturbance elsewhere. If a similar capsule enclosed the suprarenal gland or the ovary there would occur similar physical signs from enlargement of these glands.

It was not stated whether the sella turcica was small or showed erosion or faceting in the patients reported. In patients with migraine the pituitary fossa shows the results of pressure. I wish to stress this disturbance of the pituitary fossa, and agree with Dr. Brickner and his associates that the precipitating cause is an abnormality in the sella or in the hypophysis. I do not agree that the factor of inheritance is sex-linked, with respect to the ovary, in its connection with the anterior lobe of the pituitary gland. I think that the unit of inheritance is the size of the sella turcica.

I wish to mention the case of a woman with enormously involuted anterior clinoid processes. She menstruated only once or twice a year; she had been married for three or four years and had not been pregnant. She had migraine bilaterally—an occasional type. When the condition was recognized, anterior lobe of the hypophysis was administered both in desiccated form and by hypodermic injection, as she wished to become pregnant. She had not menstruated for six months; after injections for one week she began to menstruate and became pregnant. Following delivery, the headaches recurred, and the menstrual periods ceased. Again the same treatment was carried out; again she menstruated and became pregnant.

Another case, reported by Pitfield in *The Journal of the American Medical Association* (**90**:45 [Feb. 11] 1928) was that of a man who had had attacks of migraine for many years. In one of these he felt a "snapping" within his head; the headache immediately ceased and did not recur. With roentgenograms a break in the continuity of the posterior part of the sella was observed. The roentgenogram shown now is a replica of that in the case reported. The posterior clinoids are broken from the base. From this one may conclude that there is solid basis for the pituitary hypothesis.

Plaveck presented at the International Congress at Vienna two cases of migraine in which autopsy was performed. There was a rounded mass of pituitary gland on one side of the sella impinging on the cavernous sinus and impeding its activity.

DR. PHILIP E. SMITH: The factual findings reported are of great interest. They point to one more condition in which prolan in the urine does not indicate pregnancy. Dr. Kurzrok's long experience places the facts beyond question. I wish to discuss briefly the suggestion that the pituitary gland is one cause in the production of these headaches. This generalization assumes that prolan is identical with the secretory product of the pituitary gland. Otherwise no such generalization could be made. Dr. Kurzrok stated that some work has indicated that prolan is not identical with the secretion of the anterior lobe of the hypophysis. This is correct and is important in regard to speculations on the causative rôle of the pituitary gland in migraine. To be sure, in Europe it is still generally assumed that prolan is identical with the pituitary secretion. In this country, however, there is a growing mass of evidence which indicates that prolan and anterior pituitary extracts are not identical. I cannot mention all the evidence here, but will give that from three lines of work only: 1. If pituitary extract or implants of pituitary gland are given in increasing amounts, there is a proportionate increase in the ovarian response; an increase in the weight of the ovary of fifty times or more can be secured. This is not true of prolan. A certain amount of prolan will give a maximal effect, and any amount given above that does not increase the response. 2. Dr. Leonard showed that if anterior pituitary extract and prolan are standardized in rat units and then the ovulation test of Friedman is applied in terms of these units, it requires many times as much prolan to cause ovulation as is required with an extract of the anterior pituitary gland. 3. If a rat is hypophysectomized, it can be restored to an essentially normal condition if pituitary extract is given or a fresh gland is implanted. The giving of prolan does not accomplish this. It causes but little enlargement of the ovaries, and gonadal function is not restored. These three lines of evidence, to which others could be added, indicate that prolan and anterior pituitary extracts are not identical. Where prolan is formed is still a question. From the evidence given in the paper I should be inclined not to speculate on the pituitary gland as a causative factor in migraine. I find that it gives me less headache later if I do not generalize too much in print. To secure evidence of a hormonal nature which demonstrates that overactivity of the pituitary gland is a causative factor in migraine, there must be found in the blood of these persons a substance which is identical physiologically with an active principle of the pituitary gland. The facts presented are of great interest, but conclusions drawn from them are apt to be premature.

DR. BRICKNER: I wish to comment on a few of the points that Dr. Timme raised. He said that while it is true that migraine is usually associated with menstruation, it is not always associated with it, and that therefore the diagnostic criteria should not have been what they were. However, in choosing for study cases of a condition which is as vaguely defined as migraine, it is necessary to adhere to some criteria and to let others go. This is what we did. As to the preliminary symptoms of migraine, we took full cognizance of them. Every symptom of each patient has been recorded. We have not found, however, that the prodromes which Dr. Timme has mentioned are always present in the interval between the appearance of prolan and the development of the attack.

Dr. Timme also stated that prolan might not be the cause of the headache, but a by-product of some mechanism that is more essential. This may be true; I shall return to it in a moment.

Concerning the size of the sella radiographically and the question whether it was smaller than usual or malshaped, each patient was examined by stereoroentgenograms with this possibility in mind. In these cases no abnormalities of the sella were observed; there were no calcifications or other changes in the ligaments or dura around the sella.

I dislike to disagree with Dr. Timme about a point concerning which he feels that he is in particularly thorough agreement with us, but we are anxious to be clear about certain matters. I am not sure that I understand his comment. We do say and believe that there is evidence suggesting that some pituitary abnormality is related to these attacks. We do not know that this relationship is anatomic. I outlined the mechanical theory in full, but perhaps I was not clear enough in showing that we did not necessarily adhere to that theory. We thought it best to outline the various suggestions and thoughts of others which related the gland to the attacks, but we do not stand by any of them; our work is not related to them, and we do not believe that our results indicate, one way or the other, what the anatomic relation of the pituitary gland is to the attacks.

As to Dr. Smith's comments, I think that we should make ourselves clear. The view which we have tentatively developed as a result of this work is: The evidence indicates that prolan as it appears in the urine and therefore probably in the blood is related in some way to the incidence of each attack of migraine. We have thought that this is an indication, but an indication only, that the pituitary gland may be connected with the attack. Naturally, Dr. Kurzrok in particular is cognizant of the current evidence that prolan is not identical with the product of pituitary function. We shall depend on the studies of Dr. Smith and others for comprehension of the relations between prolan and the pituitary gland, and we shall continue to follow his lead.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Regular Meeting, Dec. 15, 1932

W. J. MIXTER, M.D., *Presiding*

TREATMENT OF EPILEPSY. DR. MORGAN B. HODSKINS.

As nearly as can be estimated 1 person in every 396 of the population is epileptic; according to this ratio, there are 10,731 epileptic persons in Massachusetts. The recovery rate is given as from 4 to 10 per cent. Several factors influence the likelihood of arresting epilepsy. In my experience, cases with an onset before 10 years of age are the least favorable, though they are apt to present long remissions; this tendency to remission should be borne in mind, when the value of any form of therapy is being determined. The most favorable cases from the point of view of treatment are those with the onset between the ages of 14 and 20 years. In those beginning after the age of 25, treatment is unsatisfactory. The duration of the malady has a great influence on success or failure in treatment. Arrest or improvement is more likely during the first five than during the second five years of the disease. Major attacks are more tractable to treatment; then follow combined major and minor attacks, the least favorable being minor seizures occurring alone. The frequency of attacks materially affects the success of treatment; the more frequent the seizures, the more difficult are they to control. Cases in which there is an organic change in the central nervous system are unfavorable. Heredity seems to have no effect on the course or prognosis of the disease.

Briefly, then, the case most favorable for treatment is a cryptogenic one with onset between 14 and 20 years of age, with major seizures at infrequent intervals and no mental impairment.

Treatment for epilepsy must be continued for years and often for life; hence, the measures selected must be of the type that the patients will carry out. Some measures become so irksome that they are given up after a few months, especially if the seizures are not held in check. Methods that raise the convulsive threshold are: starvation, provision of a ketogenic diet, dehydration by limitation of the intake of water and administration of drugs.

The two most useful drugs are phenobarbital and bromide; a combination of the two often gives better results than either one. If the intake of salt is limited, a daily dose of 30 grains (1.95 Gm.) of sodium bromide is generally sufficient. The daily dose of phenobarbital should never exceed 6 grains (0.4 Gm.). Even smaller doses may produce cutaneous eruptions, acute mental disturbances and incoordination.

My associates and I had the best results with what may be called a borderline ketogenic diet — one containing about 120 Gm. of carbohydrate, 60 Gm. of protein and 155 Gm. of fat. We have found it useful to limit the intake of fluid and also to combine with these two measures, phenobarbital or sodium bromide, or a combination of the two, in the proper dose for the patient concerned.

A View of Epilepsy After Ten Years of Research. Dr. William G. Lennox.

Ten years of work devoted to the problem of epileptic seizures has yielded both facts and opinions. The main pathways followed in the investigation have been as follows: (*a*) the assemblage of all possible information from modern and ancient authors; (*b*) single determinations on the blood of from 100 to 400 patients, of the nonprotein, urea, amino-acid and uric acid nitrogen, calcium, chloride, sugar, blood sugar curves, fibrin, sedimentation rates, bicarbonate and gases, the last in blood drawn from an internal jugular vein, a femoral vein and an artery; (*c*) determinations of the pressure and the sugar, chloride, calcium and protein content of the spinal fluid; (*d*) determinations of the basal metabolic rate; (*e*) day by day or serial observations of small groups of patients in whom the effect on seizures and on metabolic processes was noted for such procedures as fasting, adherence to a ketogenic diet, ingestion of acids, dehydration, alterations in the composition of respired air and increase in the atmospheric pressure; (*f*) study of psychologic histories of patients; (*g*) experiments with animals on the use of convulsive drugs and on the effect on pial vessels of altering the gaseous content of the blood; (*h*) observations of the cerebral circulation in patients and of the effect on the circulation of mental work, injection of histamine and breathing of various mixtures of gas; (*i*) a statistical study of the records of 1,500 noninstitutional patients.

Of these various lines of investigation, probably the most distinctive has been the demonstration that seizures may be influenced by alteration of certain physicochemical processes in the body (particularly of the supply of oxygen), and that the cerebral circulation is profoundly influenced by the content of oxygen and carbon dioxide in the blood (the brain being supplied with arterial-like blood at the expense of the extremities).

As important as the gathering of new knowledge is the utilization of knowledge possessed. Three aspects of the problem of epilepsy need emphasis: 1. In the epileptic patient one must look, not for the cause, but for the causes. The epileptic person resembles a reservoir which periodically fills and overflows in a convulsion. Five main subterranean springs may feed this reservoir. Most fundamental is the patient's natural susceptibility or tendency to seizures, terms which may be translated as "heredity" or "idiopathic sensitivity." This tendency is probably present to some degree in every patient subject to seizures, no matter what pathologic condition also exists. A family history of epilepsy is obtained in only one fifth of the cases; it is not seizures but the tendency to seizures that is transmitted. An inherent susceptibility is present in most medical conditions, whether these are symptoms — sneezing or headache — or disease entities — tuberculosis or cancer. Next in importance is a lesion of the brain, though only one fifth of noninstitutional

patients present neurologic evidence of a cerebral lesion. A person who is a near relative of an epileptic patient is about one half as likely to have seizures as is a person with an injury to the brain and one tenth as likely as a person with a tumor of the brain. Physical abnormalities outside the central nervous system, disturbances of the sympathetic nervous system and emotional disturbances are other groups of causes. In a patient with seizures, not one but several of these factors may ordinarily be demonstrable. Logical treatment consists both in blocking the channels of inflowing influences and in raising the patient's threshold for seizure. The tragedy for the patient is that he is often treated by a succession of specialists each of whom sees but a single aspect of the total problem.

2. The relationship of physical abnormalities or of events to the seizures must be carefully defined. Concerning each event (whether emotional or physical trauma, ingestion of a food, constipation or the like) three possibilities must be considered. Is the abnormality a coincidence? Is it a result of seizures? Is it a cause? In the last case, is it one of several cases, or the only one? With reference, for example, to emotions, one must remember that the average epileptic patient has had hundreds of seizures. Events which preceded one or a dozen of these may be coincidental or may play such a small part in the total that they deserve little emphasis. Account must be taken likewise of the many occasions on which the apparent precipitating cause was present in unusual force without a seizure resulting. In order to judge the relative numerical importance of precipitating factors such as constipation or emotional storms, inquiry should be made as to whether the abnormal condition is more frequent in epileptic than in healthy persons or in patients with chronic conditions of the joints or heart. Hysterical seizures in which emotions determine not only the time but the pattern of the convulsive manifestations have almost gone out of the picture. Emotional conflicts which are mostly on the conscious level, such as financial worries, interfamily conflicts, disappointed ambition or unrequited love, appear frequently as apparent contributing or precipitating causes. The importance of the physiologic mechanisms joining emotions and immediately occurring seizures, as well as the therapeutic importance of eliminating discords, is obvious. Psychiatrists who believe that deeper and more obscure reactions, such as the wished-for security of intra-uterine life, the pleasure of sucking and the love of mother, may somehow years later terminate in seizures, seem to be treading ethereal pathways.

3. A seizure originates only in functioning nerve cells. It cannot originate in a dead cell, in scar tissue or in a psychologic complex. If such abnormal structures could act on a healthy cell to produce a seizure, one would expect seizures in every case of trauma or tumor of the brain and in every psychoneurotic person. Crudely expressed, a nerve cell presumably functions as does an electric storage battery. Conceivably, conditions which impair the efficiency of a living electric cell (changes in the supply of oxygen, water and electrolytes or in the oil film about the cell) result in loss of consciousness, the essential portion of the seizure, and, less frequently, in release of convulsions. Conditions which alter the chemistry of the nerve cell, such as changes in oxygenation, hydration and acid-base equilibrium, are the conditions that have been found to influence seizures. This field of study offers great hope for an extension of knowledge. There are many links in the chain of events leading to a seizure. Further clinical, pathologic and biochemical knowledge must be accumulated and synthesized.

INFLUENCE OF EMOTION IN PRECIPITATING CONVULSIONS. DR. FRANK FREMONT-SMITH.

Emotion has often been mentioned as one of the immediate causes of convulsions. Gowers (1901), in a study of 1,665 epileptic patients, found over 230 cases in which "fright" was given as the inciting cause for the first seizure. During the past three years an effort has been made to determine how frequently emotional tension acts as a precipitating factor. Thirty-six unselected private patients were studied. The ages varied from 10 to 53 years. All suffered from generalized convulsions

with loss of consciousness. In 24 of these patients a direct relationship has been found between emotional tension and one or more of the major convulsions. In several, all or nearly all the attacks have been immediately preceded by strong emotion: usually fear, guilt or frustration. That the emotion has a causal relation to the convulsion is indicated by the fact that in 8 patients major or minor attacks have been precipitated under observation by a discussion of the emotional difficulty. In 3 patients attacks could apparently be precipitated at will by such discussion.

This group of 24 patients includes some with no history of mechanical or infectious trauma to the brain, and no evidence, on examination, of a pathologic condition of the central nervous system; others with definite history of such trauma, with or without evidence of abnormality on examination, and still others without a history of such trauma but with definite evidence, on examination, of a pathologic condition of the central nervous system.

In the light of these observations, one may conveniently divide the causes of convulsions into predisposing factors and precipitating factors. Organic disease of the brain is frequently a predisposing factor. Emotional tension is often a precipitating factor. Some patients realize that their attacks are precipitated by emotional tension. Often, however, the patient is unaware of this relationship until it has been brought out through a series of discussions. An understanding by the patient of the significance of emotional tension in precipitating the seizures, together with a better adjustment of the major emotional conflicts, has proved of definite therapeutic value. Psychoanalysis and other forms of emotional reeducation have been used with encouraging results.

The physiologic mechanism by which emotion can precipitate a convulsion in a predisposed person is of particular interest and deserves study. That stimulation of the sympathetic nervous system by the emotions plays an important rôle is supported by the fact that convulsions are occasionally precipitated by pain and by cold. Emotion, pain and cold are well known stimulators of the sympathetic nervous system. Moreover, the onset of acute infections frequently precipitates convulsions in predisposed persons. Here again the sympathetic nervous system is strongly stimulated. Whether the stimulation of the sympathetic nervous system precipitates the convulsion by cerebral vasoconstriction or by some other mechanism is not known. A strong case can be made for the theory of vasoconstriction, but the evidence is not conclusive.

Summary.—In 24 of 36 private patients suffering from generalized convulsions, emotion was a precipitating factor; in 8 patients, major or minor seizures were precipitated by emotion under observation; evidence is brought to show that the emotion acts through stimulation of the sympathetic nervous system.

DISCUSSION ON PRECEDING PAPERS

DR. WALTER B. CANNON: One of the wisest remarks made by Dr. Lennox was that plurality of causes should be regarded. That is a possibility that we are likely to overlook.

I am interested in the cases that Dr. Fremont-Smith reported. It has been suggested that the symptoms were caused by strong emotion operating through the sympathetic system on peripheral arteries and causing spasm in them — for example, in the brain. There is also the possibility, however, that strong emotion, having its neural basis in the diencephalon, might discharge impulses directly to the cortex. This would be in keeping with the extraordinary observations of the Russian psychiatrist, Luria. He has devised an arrangement whereby a person to be examined applies each hand to a rubber bulb so that a slight pressure of the fingers is registered on a moving surface. When a word is spoken, the subject in return speaks the first word that comes to his mind and simultaneously presses *one* bulb. If words to which the subject is indifferent are spoken, he may show perfect coordination between talking and pressing the single bulb, but the coordination disappears if there is much excitement. If he is not indifferent to the word-signal, but feels it awaken an emotional experience in him, he may hesitate

a relatively long time, press *both* bulbs and show other signs of diffuse discharge of nerve impulses. May the epileptic attack not be an exaggeration of a process that all of us have experienced?

Another point to consider is that the emotional response can be conditioned, just as in dogs the salivary flow can be conditioned, by association with any stimulus. The situation is similar when a person has had an emotional experience and a convulsive attack; anything that brings back the original circumstances may also bring back the attack, because these circumstances make the conditioned stimulus. Still another point is that, besides emotion, cold and fever may affect the neural mechanisms in the diencephalon. Likewise, pain may be influential and also lack of oxygen. On the latter point, the observations which Dr. Lennox has made would fit in with those made by Dr. Fremont-Smith. I believe that a more optimistic stand might be taken concerning treatment for epilepsy. In the last few years an advance has been made by means of a ketogenic diet and dehydration. The profession may yet have a better grip on the whole situation.

Dr. Stanley Cobb: I may add a word about vascular spasm, which is only one theory of the etiology and explains a certain number of seizures. This has often been observed by surgeons. Foerster has observed vascular spasms of the exposed cerebral cortex in over one hundred epileptic patients in whom the brain was explored under local anesthesia. I have observed it at least twice. A patient whose brain was being explored by Dr. Penfield under local anesthesia began to have a seizure. At the onset there was a pale spot almost in the motor area, then another posteriorly, which afterward spread into the first. As the seizure progressed, the whole brain became blue, but the white spot stood out for a minute and a half — a long while, in view of the cerebral congestion — conspicuous in the middle of the congested brain. Thus there is absolute evidence of a cerebral vasoconstriction; from the etiologic standpoint it may well correspond to the oxygen-lack which Lennox has emphasized and to the emotional episode which has been found to be a precipitating factor by Fremont-Smith.

Let me emphasize once more that epilepsy is a symptom with many underlying and precipitating causes. It cannot be called a disease, any more than headache can be called a disease. All the word epilepsy means is that the patient has recurrent seizures.

Book Reviews

Psychopathology of Forced Movements and the Oculogyric Crises of Lethargic Encephalitis.* By Smith Ely Jelliffe, M.D. Price, $4. Pp. 215. Washington, D. C.: Nervous and Mental Disease Publishing Company, 1932.

Dr. Jellif(f)e's monograph on the "Psychopathology of Forced Movements in Oculogyric Crises" presents an attempt to understand these movements "in the light of psychopathologic reactions to traumas of the brain" (p. 193). Jellif(f)e shows with good authority that one cannot hope to discover the explanation of these "forced movements" unless they are studied from a dynamic, purposive aspect. "Is it not of paramount importance to study motivation, as well as movements?" (p. 198), he asks, and reminds us of Maudsley's statement that an "organ is a bit of structuralized experience." In other words, if one wishes to understand these phenomena one must enquire into their meaning, realizing that though the organism has been injured, it still functions as a unit. To give a simple analogy, one might compare such phenomena as are seen in a postencephalitic patient with the flight of a wounded bird. The bullet wound might explain the drooping wing, but it could not explain the peculiar irregular course of the bird's flight. Here the reader is referred to the well chosen citation from Whitehead, pp. 159 and 180, and the discussion that follows.

Having established this thesis, the author proceeds to examine the form and psychic content in cases reported in the literature, including those which he has investigated at length himself. He points out the similitude between the oculogyric crises and the attitudes adopted in religious and ecstatic states, or in states of fear. Associated with such eye movements is often found compulsive ideation. In certain cases these ideas, as also in compulsive neurotics, are of a sexual or anal-sadistic nature; e. g., one of the patients had the compulsive tendency to stare at men's trousers (where they are buttoned) (p. 139). The idea, however, only came into consciousness about the time when the oculogyric crisis ceased. The author draws the conclusion in general that the ocular spasm is only "a part of a complicated generalized defensive effort of some sort." In these crises there is a slowing up or "stickiness" of the thought processes. The author states: "One thing is evident, that the thought repressions are not due to somatic impairment solely any more than are the ocular spasms, for during the intervals in which the patients are well no such phenomena are present. . . . (".) This, of course, is a very unsound conclusion. One does not know what organic changes occur in the brain during the period of (the) crisis. The author continues: "Hence our inference that repression is operating here at psychological levels just as inhibition operates at lower physiological levels." This is merely an assumption which has not been proved (parallelism has no more logical foundation than Spinoza's theory of the grandfather clocks).

The affective states during the crises vary considerably. Often anxiety prevails. The author attempts to correlate the affectivity with the mental content. He points out that few serious studies have been made on the subject. Consciousness is often impaired. "A complete garment (gamut) of stages of awareness from full vigilance to absolute psychical blocking or even to unconsciousness are observable. . . ." Often the patient expresses the desire to go to sleep. Dr. Jel(l)iffe attempts to correlate Head's conception of the "vigilance" (p. 160) of the decerebrate animal with Freud's conception of the "unconscious." The author here falls into the error of comparing an anatomic conception of the psyche with a psychodynamic one which is topographically expressed. Freud specifically rejects any such comparison.

* Dr. Jelliffe's corrections are in parentheses. This does not apply to page numbers.

The cases which have been investigated by the author personally are for the most point (part) disappointing, and fail to throw any conclusive evidence on the psychic dynamics of these phenomena. Of course one may often observe in other cases of organic injury to the brain, such for instance as in dementia paralytica, that the underlying neurotic attitudes or infantile trends are uncovered. So here also one may observe various unconscious trends at play. But do they have anything specific in explaining the oculogyric crises or their purpose?

Nowhere does Dr. Jel(l)iffe give a concrete, straightforward statement of his psychodynamic conception. One must search through the entire monograph to understand what he is driving at. He most closely approximates to this on page 204. In general his conception may be expressed as follows: The ego has been weakened by the traumatic brain lesions, consequently instinctive drives are less adequately inhibited. A struggle is set up between the repressing and repressed forms of energy. "Symptoms arrive to release the suppressed energy and save the individual from further regression. . . ." There is an attempt on the author's part to correlate various trends in modern scientific and philosophic speculation; e. g., Head, Bergson, Whitehead and psychoanalysis. His views are couched in psychoanalytic terminology. However, in making use of this, we feel he has a somewhat superficial understanding of analysis. Certainly as far as the analytic terminology is concerned there are many errors. For example, on page 167 he speaks of the sublimation of the repressing forces when presumably he means a sublimation of the repressed forces.

Again, on page 194 Jellif(f)e states "In mankind and the creatures related to him the action of parturition appears to be the first individual anxiety experienced to give the characteristic traits of the anxiety aspect. It is not to be supposed that Ranke's (Rank's) thesis on the birth trauma is here upheld in toto." We wish here merely to point out in passing that the entire book "Inhibition, Symptom and Anxiety" by Freud was written about this question, and that the statement here quoted gives a wrong impression. Again he says "The first intense outburst(s) of anxiety in childhood, at any rate, seemed (seem) to follow the differentiate (ion) of the superego." That is to say they follow the passing of the Oedipus situation, for the superego is the heir to the Oedipus conflict. It is of course exactly the opposite, namely, that the anxiety during the Oedipus situation gives rise to the superego. In general, we may say that Jellif(f)e's entire conception of the structure of the psyche is very much more rigid and topographically differentiated into pigeon-holes than is that of Freud('s). On the other hand, it is doubtful if he throws any enlightenment on the subject by attempting to correlate these forced spasmodic movements with tics or compulsions. It may well be that ideas of a compulsive nature exist along side the compulsive movements(,) but proof is lacking that they have a direct causal relation, or that they play a part in the etiology.

As regards the wealth of clinical material, description of cases, historical research and interesting case material, the reader will be well repaid by perusal of his book; and it may be stated that Dr. Jellif(f)e's approach toward the subject will certainly form a basis for further investigations.

REPLY BY DR. JELLIFFE

The foregoing review was submitted to Dr. Jelliffe, who replied as follows. The review and the letter are published with the permission of the reviewer and of Dr. Jelliffe.

"Many thanks for letting me see the review. It is both interesting and amusing from the manifest as well as from the latent content.

"I am quite prepared to be told and even to entertain the notion seriously that my knowledge of psychoanalysis is quite 'superficial,' but at the same time I am not surprised to believe that this is, as yet, a more or less universal situation.

"My observation also has led me to note that this seems the general viewpoint of every analyst about every other analyst and leads to interesting reflections upon the Jehovah complex which we all share. The younger the analyst the more he

seems to see the deficiencies of his fellows. Every new crop from Europe or, of late, from some local shrine, fairly bursts with their 'enlarged vision' of the theory of psychoanalysis. It takes 20-30 years of analysis and possibly 60 years of life to realize how 'superficial' our real understanding is.

"I do not see any reason why the critique should not be published. I think it shows up the writer's inadequacies more glaringly—even within its own construction—than it does mine. I could say from the short series of notes it contains that the writer had not really read the book carefully nor understood its purport. There are misstatements. He fails to distinguish an effort at 'explanation' or 'elucidation' or 'illustration by analogy' and calls such attempts at 'correlation.' Thus so far as Head's vigilance conception is concerned, I would say the writer had little acquaintance with Head's notions in the first place, and evidently little understanding of the use made of them—up to a certain point—in my exposition. His statement that an 'anatomical conception of the psyche is confused with a psychodynamic' one is just dense.

"When I said 'an inference may be drawn'—he calls this a faulty 'assumption' and the comment about 'organic' changes taking place during a crisis is very nonsensical. If he had taken the trouble to note my use of Jackson's conceptions of positive and negative signs, as related to 'destructive' lesions, he would not have written as he did. Furthermore I talk of 'reversible and irreversible' organic changes, never of 'organic' changes. Organic changes are always taking place in all functioning organs. Any one should know that; whether within the physiological range and whether reversible or not is the important consideration.

"I am glad to know that the critic thinks he knows what Freud rejects. He would be instructed if he could read Freud's correspondence with me about these very studies. He probably would not look for 'my' psychodynamic conception. Page 195 (not 194 as stated by the critic) is a direct quotation from Freud's 'Inhibition' paper—hence how can it give a wrong impression? I fear the critic here is being a 'smarty' and does not know the 'Inhibition' study as much as he pretends to know, even with its vile translation. The Super Ego as the 'heir' to the Oedipus complex is a statement made over and over again by Freud.

"As to my own conception of the psyche I wish I knew it as well as the critic seems to. I confess with my advancing years it gets more and more difficult to verbalize and I would be pleased to learn from his lips or his writings the many things I am seeking to find out about the human being.

"One little bit of faulty type reading amuses me. The critic would extend his castration to my name. He fails to correct his typewritten copy when twice the letter (f) is omitted, then twice the letter (l) is omitted, then three times the letter (f) is omitted. I suspect a 'stuttering complex' somewhere.

"I see no objection to printing the review especially as an 'exhibit'; at all events I have been a banderilla performer for many years and whether my darts have been directed at the critic or not it is only fair that I should get a thrust now and then."

(signed) SMITH ELY JELLIFFE.

The Psychological Effects of Menstruation. By Mary Chadwick. Price, $2. Pp. 70. Washington, D. C.: Nervous and Mental Disease Publishing Company, 1932.

To the reader familiar with freudian terminology and convinced of the adequacy of the psychoanalytic hypothesis, this book will prove interesting. One not well versed in the technical language of the analyst, however, will find it almost unintelligible. It is the author's purpose to determine the psychologic mechanisms associated with menstruation by a research into the symptoms which arise or become aggravated during the monthly period, by a study of the associated phenomena of transference, by an analysis of the dreams and fantasies which appear at that time and by a survey of the sociologic influences affecting the menstruating girl.

The book opens with a historical review of the subject, stressing particularly the ideas of horror and guilt which have surrounded the menstrual period from the earliest times, pointing out the taboos and superstitions to which these ideas have led, and tracing their residuals in many contemporary thoughts on the subject. The ancients attributed periodic psychic disturbances in women to wanderings of the uterus, while the medieval sages blamed these phenomena on the influence of witchcraft. The blighting of crops, causing mares to miscarry, souring wine and similar misadventures attributed at that time to the evil eye of the witch are strangely similar to the traditional effects of the touch of the menstruating woman. The witch may be considered a mother substitute, and witch persecution a displaced form of revenge against the mother. The characterization of the witch as a stealer of children is possibly a representation of the envy that a little girl feels toward her mother because of the latter's ability to bear children.

A woman accepts periodic bleeding as evidence of physical inferiority, an overt manifestation of the castration wound, a form of self-punishment for mother hatred and possibly as a narcissistic reaction toward a revenge wish against either parent. This first appears during the girl's childhood when, at the time of the mother's period, the routine of the household changes perceptibility. The parent becomes irritable and negligent, and these experiences cause anxiety in the child and strengthen fantasies of castration, guilt and punishment. The first menstrual period serves to destroy the subconscious hope of becoming a boy and revives the feelings of gulit, the sense of inferiority and the struggle over cleanliness which had appeared at an earlier age. The flood of associations with blood becomes overwhelming; the idea that bleeding means a cutting out of a part of the body is reestablished, and with it the representation of a menstrual bleeding as a symbol of childbirth (cutting something out of the body) and perhaps even the primitive childish fantasy that the nursing baby is sucking the blood of the mother.

The major psychic disturbances accompanying the period are melancholia, distorted attachments, a negative attitude toward other women and feelings of cruelty. The melancholia relates to disappointment over parental love, with repression of the aggressive tendencies. On the other hand, sadism may be manifested either toward the brother (of whose sex she is jealous) or toward the mother (as castrater or as inamorata of the beloved father). Sometimes the patient may demand sympathy and affection and become attached to a female friend. More often, however, the attitude toward all women is a negative one, all of her own sex being considered castraters or rivals.

Among the many fantasies and dreams which occur at the time of the menstrual period are thoughts of kidnaping or killing infants (envy over other women's child-bearing capacity); the fear of being poisoned (a descendant of the trauma of weaning, the representation of the hostile mother who would deny the baby food); fears of being drowned in a flood, destroyed by an earthquake or swept away by a tremendous cosmic force, which are all manifestations of the fantasy of birth; dreams associated with sexual relations, such as ideas of having intercourse with the father or with animals (menstrual sleep-walking is said to be a prostitution fantasy), dreams of pregnancy, and finally dreams of suicide and death. The methods of suicide contemplated or actually chosen are often symbolic, and the very common desire to throw oneself into a body of water or to make use of the gas oven is unmistakably a fantastic return to the mother's womb.

The book is closed with a short discussion of the psychology of the menopause. Its principal characteristic is the hostility toward men so often displayed by women at the climacteric. This is presumably a compensation for the desire to be a man which is revived at this time.

In an appendix the author reports two case histories which show in their prevailing symptoms fantasies, dreams and manifestations of transference which three centuries ago were considered typical of women who were accused of witchcraft. Today they would be considered characteristic of overwhelming mother fixation.

Das Rechts-Links Problem im Tierreich und beim Menschen. By Wilhelm Ludwig. Price, 38 marks. Pp. 496. Berlin: Julius Springer, 1932.

Ludwig reviews the findings with regard to all bodily asymmetries. From the study of asymmetries of the upper extremities, he concludes that in three fourths of the cases the right is longer, larger or stronger, and usually all three. Asymmetries of the lower extremities are less frequently studied, because the problem of handedness is not directly involved. The differences in the lengths of the extremities are slighter in apes.

Ludwig defines handedness as an innate disposition to carry through finely coordinated movements more easily, more rapidly and more effectively with one hand than with the other. As a consequence of this disposition, the favorite hand is used more intensively in daily life than the other hand, and in all natural behavior which requires the cooperation of two hands it takes over the more difficult part. From various studies Ludwig estimates the frequency of left-handedness in males as from 4 to 5 per cent. He finds that the condition is about half as frequent in females.

Handedness preferences appear about the seventh month. Ludwig concludes, mostly from Stier's findings, that after puberty there is a tendency to exclude favoring of one hand, the right in the right-handed and the left in the left-handed, and that secondarily the arm most frequently used will be the stronger. Ludwig thinks that the inheritance of left-handedness may be established statistically. In general, left-handed persons have a greater tendency to left-handedness in their families than right-handed persons have. He thinks that the law of inheritance cannot be formulated, but that it is a mendelian mechanism.

As to the pathology of left-handedness, Stier first pointed out in 1911 that among persons with speech defects, especially stutterers, there is a large percentage of left-handedness. He also showed that among the soldiers he examined the left-handed showed about twice as many signs of degeneration; they were generally less useful in the service, and they had less prospect of being advanced. There were more left-handed persons in the prisons, and certain physiologic signs of degeneration, especially poor endowment, were much more frequent among left-handed than among right-handed persons.

Leggedness or footedness, like handedness, is an innate disposition to prefer one leg in all activities which are carried out by one leg or in which one leg can play a leading rôle. Leggedness appears at the age of from 4 to 7 months, and is very clear at 2 years.

From a survey of the findings on eyedness, Ludwig concludes that 98 or 99 per cent of men are either right-eyed or left-eyed.

This work summarizes well the current knowledge of right-handedness and left-handedness.

The Process of Human Behavior. By Mandel Sherman and Irene Case Sherman. Price, $30. Pp. 227. New York: W. W. Norton & Company, Inc., 1929.

This book purports to be based on the authors' clinical observations of infants and young children. Some of the actual observations presented in chapters 3 and 4 on the development of sensorimotor activities are of interest; e. g., responses to pain appear earlier in the anterior (upper) end of the body, and develop more rapidly than those in the posterior (lower) parts. The majority of infants below 20 hours of age are unable to make a perfectly coordinated defensive movement of the two arms and hands. Infants as old as 320 hours (somewhat over 13 days), however, are still unable to make an immediate perfectly coordinated defense reaction of the two arms. Chapter 5 is valuable because attention is drawn to the fact that the evaluation of a child's emotional response to a situation is usually in terms of the observer's response to the situation. Such clinical material is of value, and if published in the form of two or three scientific papers would make a

worth-while contribution. Here it is interspersed among a mass of material which is either so well known as not to require repetition or lies in the realm of the highly controversial. The chapter titles are as follows: (1) "The Growth and Importance of the Nervous System in Animals and Man;" (2) "The Functional Significance of the Human Nervous System"; (3) "The First Human Responses"; (4) "The Relation of Sensori-Motor Development to the Growth of Intelligence"; (5) "The Observation of the Emotions"; (6) "The Nature of the Emotions and Their Influence upon Behavior." They indicate that the authors have had the ambition to cover the whole problem of human behavior and as a result have produced a book which is sketchy and unscientific, not adapted to the professional or scientific reader and dangerous in the hands of the layman because it offers under the guise of scientific knowledge a number of highly disputed points with all the assurance of a scientific dictum and just enough of fact to becloud the issue. The book is not to be recommended.

Neuropathology: The Anatomical Foundation of Nervous Diseases. By Walter Freeman, M.D., Price, $4. Pp. 350. Philadelphia: W. B. Saunders Company, 1933.

A small and comprehensive work on neuropathology in the English langauge has been needed for a long time. There are many such works in the German literature. The present volume consists of 13 chapters and 349 pages. The treatment of the subject is well handled. The book begins with a discussion of the cytology and cytopathology, and then treats in order the meninges, vascular disease and arteriosclerosis, inflammations, tuberculosis, syphilis, leprosy, intoxications, injuries, the functional psychoses, malformations, degenerations and intracranial tumors. Necessarily no particular subdivision is treated in extenso. For example, tabes is discussed in 2 pages, but the description should be considered as part of the general subject of syphilis. Tumors of the brain are discussed in 23 pages. The discussions are adequate and give the student an excellent description of the pathology of the nervous system. The illustrations are excellent. Practically all of them are original, although here and there acknowledgment is made of illustrations borrowed from others. There is a useful reference at the end of each chapter, and a glossary.

The book is an excellent illustration of the progress which has been made in the knowledge of the pathology of the nervous system. This has been largely because of the new staining methods which are the outgrowth of the last two decades. Nevertheless, the discussion of the functional psychoses is depressing, for, as the author states, the neuropathology of functional psychoses is yet to be written.

Diagnostik der Hirngeschwülste. By Kurt Goldstein and Hans Cohn. Price, 12 marks. Pp. 138. Berlin: Urban & Schwarzenberg, 1932.

The exact diagnosis of tumors of the brain depends largely on the recognition of early symptoms. Most patients with tumors come to the attention of neurologists and neurosurgeons when the symptoms have progressed so far that an exact diagnosis is not always possible, at least, by neurologic symptoms alone. As a consequence, the mechanistic aids which have been employed and developed in the course of the last two decades have to be used. In the recent literature most books on tumors of the brain have been written by neurosurgeons. The volume under review is by neurologists. Necessarily, in 130 pages it is impossible to discuss symptomatology at length, but emphasis is chiefly laid on early diagnosis.

The book is divided into two parts: general and special. It is interesting that in the general discussion there are ten divisions, this emphasizing, perhaps, as much as anything else the increase in knowledge in the last two or three decades. The divisions are as follows: (1) general symptoms; (2) pressure symptoms; (3) choked disk; (4) psychopathologic disturbances; (5) physical methods of examination;

(6) puncture; (7) roentgenology; (8) ventriculography and encephalography; (9) ophthalmologic and otologic examinations, and (10) rhinologic, hematologic and serologic examinations.

There is nothing particularly new in the special divisions except that frontal and cerebellar tumors are discussed together. There is no particular reason for this, for it is only rarely that frontal tumors produce cerebellar symptoms. This book does not present anything especially new, but it does emphasize particularly the early diagnostic measures.

Humoral Agents in Nervous Activity, with Special Reference to Chromatophores. By G. H. Parker, Harvard University. Price, $1.75. Pp. 79, with 19 illustrations. New York: The Macmillan Company, 1932.

Thirty years ago Bayliss and Starling discovered secretin, the first hormone to be described. This introduced the conception of humoral as contrasted with nervous control. In this book, Professor Parker utilizes many salient facts about the behavior of chromatophores in cold-blooded vertebrates and the Crustacea of the invertebrates from the contrasted points of view of nervous and humoral control. When denervated, fish chromatophores still react to epinephrine. Amphibian melanophores are controlled by varying amounts of pituitary intermedia secretion rather than by nerves. These are examples of humoral control of this type of effector, in the apparent absence of nerves. The author then advances the idea that when nerves are present they may secrete something which is the real activating agent. This would be formed at synapses and other nerve terminals. In the giant fibers of the earthworm there are macrosynapses, which consist of an oblique apposition of the terminals of dendrite and axon. Of the two elements in the synapse, the dendritic element stains more deeply with osmic acid than the axonal element. This observation is adjudged to indicate a possible secretory function of the dendrite terminal. This, then, is the humoral agent in nervous activity. The author discounts the aphorism that the brain secretes thought, but is strongly inclined to the idea that nervous secretions may play a part in mental operations.

Etudes neurologiques. By Georges Guillain. Fifth series. Price, 80 francs. Pp. 462. Paris: Masson & Cie, 1932.

The fifth volume of reprints from the Neurologic Clinic of the Salpêtrière, under the leadership of Professor Guillain, contains forty-four papers. As in its predecessors, the papers are divided into groups: (1) cerebral tumors; (2) the pathologic changes in encephalitis; (3) diseases of the brain stem and cerebellum; (4) the spinal cord; (5) the cranial nerves and rachitides, and (6) various syndromes. Lastly, there is an appreciation of Charles Foix. This is the usual classification adopted in the previous volumes, with minor changes here and there. With the exception of the advances that have been made, particularly in neuropathology, the work varies little. On the whole, it is a credit to the French literature and to the Salpêtrière, which was made famous by the work of Charcot and Pierre Marie.

Hydrotherapy in Hospitals for Mental Diseases. By Rebekah Wright, M.D. Price, $3. Pp. 396. Boston: The Tudor Press, Inc., 1932.

So far as the reviewer is aware, this is the only book that has been published in recent years dealing exclusively with hydrotherapy. Its objective is to present in concise detail the technic of hydriatic procedures that have proved practicable in the Massachusetts Department of Mental Diseases. The material is divided into four parts. The first is for the benefit of nurses, instructors and hydrotherapeutists; the second for hydrotherapeutists; the third for physicians, and the

last, for superintendents. There are ninety-two illustrations, practically all of them original. The subject is well presented, and the illustrations are everything that is desired. This work should prove to be of the utmost help.

The Cardiac Output of Man in Health and Disease. By Arthur Grollman. Price, $4. Pp. 325. Springfield, Ill.: Charles C. Thomas, 1932.

The author has succeeded admirably in bringing together and attempting to correlate the knowledge at present available relating to the output of the heart in man. The various methods that have been or are being used at present are described, and the technic of the acetylene method is given with great detail. The author obviously thinks that the acetylene method, as developed by himself, is the method of choice in this particular field of study. Data are furnished in a wide variety of physiologic and in some clinical conditions. In view of the widening scope of significance of the cardiac output this book should prove of interest to the internist and the neurologist, as well as to the physiologist.

Poliomyelitis. A Survey made possible by a grant from the International Committee for the Study of Infantile Paralysis organized by Jeremiah Milbank. Price, $6. Pp. 652. Baltimore: Williams and Wilkins Company, 1932.

This book offers a summary of the knowledge of poliomyelitis. It has been made possible by a grant of $280,000 from the Jeremiah Milbank Fund; the work has been done under the auspices of the International Committee for the Study of Infantile Paralysis and represents the results of a four year survey. Such a compilation as this is always of value. It shows that considerable progress has been made in the knowledge of the disease. The specific cause, however, as well as the manner of its communication, still remains an unsolved problem.

Lehrbuch der Nervenkrankheiten für Studierende und praktische Ärtze in 30 Vorlesungen. By Robert Bing. Fourth edition. Price, 25 marks. Pp. 570, with 190 illustrations. Berlin: Urban & Schwarzenberg, 1932.

The fourth edition of this work differs little from its predecessor, although alterations have been made here and there to bring the work up to date. There have been few changes in the illustrations. This is not a textbook in the accepted sense of the term; it is more a series of articles on various subjects, in which the discussions are adequate, but not full. For example, the subject of tumors of the brain, including both cerebral and cerebellar tumors, takes fifty pages, and aphasia, apraxia and agnosia seventeen pages.

Outline of the Cranial Nerves. By John Favill, A.B., M.D., F.A.C.P. Price, $2. Pp. 106, with 14 illustrations. Chicago: University of Chicago Press, 1933.

The author rightfully considers that the cornerstone of clinical neurology is knowledge of the cranial nerves, and in this small book he gives an adequate presentation of this subject. Each nerve is considered under five heads: (1) anatomy, (2) function, (3) tests, (4) pathology and (5) localization. The motor nerves are traced from the nucleus outward, and the sensory from the periphery inward. The illustrations are adequate. The book can be recommended for students.